ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 199 1969

TAPE RECORDINGS OF THE ELECTROCARDIOGRAM IN NEWBORN INFANTS

BY ILKKA VÄLIMÄKI

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

TAPE RECORDINGS OF THE ELECTROCARDIOGRAM IN NEWBORN INFANTS

ACTA PAEDIATRIA SCANDINAVICA

SUPPLEMENT 199 1969

From the Cardiorespiratory Research Unit, the Department of Physiology and the Children's Hospital of the University of Turku, Turku, Finland

TAPE RECORDINGS OF THE ELECTROCARDIOGRAM IN NEWBORN INFANTS

BY

ILKKA VÄLIMÄKI

CONTENTS

INTRODUCTION

At birth a haemodynamic revolution occurs in the circulation. A series of integrated events follow each other within a couple of minutes the aeration of the lungs is accompanied by the inception of functional pulmonary circulation the placental circulation ceases and the ventricles of the foetal heart, coupled in parallel, are reconnected in series by means of the closure of the foetal circulatory shunts, the foramen ovale and the ductus arteriosus. These perinatal cardio-pulmonary adjustments are the largest of the entire human life. A delay or inco-ordination of this transformation may have serious consequences. The magnitudes of both depolarization and repolarization deflections of the electrocardiogram, are proportional to the myocardial muscle mass, and reflect cardiac cell metabolism. Thus, information about the adaptation of the heart to the haemodynamic changes can be obtained from the electrocardiogram.

In obstetric departments and neonatal wards there is a tendency towards more and more intensive observation and therapy of newborn infants. The important primary functions, respiration and heart action, are to be continuously monitored. It is thus essential for correct diagnosis to know the limits of the normal variation of these functions, and also features typical of pathological conditions. This presumes the use of long term recordings in research work.

Continuous electrocardiographic and heart rate recordings without affecting the activities of the subject, are produced in two main ways 1 using a miniature electrocardiographic transmitter attached to the patient, and a special receiver for detection and reproduction of the signal (radiotelemetric instruments), or 2 employing a small portable electrocardiographic tape recorder connected directly to the patient. A third method, applicable also to these two apparatures, is to conduct the electrocardiographic signal directly to a computer where the information can be processed automatically but this can scarcely be realized in most hospitals at the present time.

The purposes of the present investigation are, to define a suitable and interference-free electrocardiographic tape recording technique for small infants; to study peculiarities in the signal reproduction of tape recording equipment, and to determine the alteration of the heart rate and the electrocardiographic signal postnatally in full term and premature infants, with long-period recordings beginning on the first day of life.

INTRODUCTION

At birth a haemodynamic revolution occurs in the circulation. A series of integrated events follow each other within a couple of minutes the aer ation of the lungs is accompanied by the inception of functional pulmonary circulation the placental circulation ceases and the ventricles of the foetal heart, coupled in parallel, are reconnected in series by means of the closure of the foetal circulatory shunts, the foramen ovale and the ductus arteriosus. These perinatal cardio-pulmonary adjustments are the largest of the entire human life. A delay or inco-ordination of this transformation may have serious consequences. The magnitudes of both depolarization and repolarization deflections of the electrocardiogram, are proportional to the myocardial muscle mass, and reflect cardiac cell metabolism. Thus, information about the adaptation of the heart t the haemodynamic changes can be obtained from the electrocardiogram.

In obstetric departments and neonatal wards there is a tendency towards more and more intensive observation and therapy of newborn infants. The important primary functions, respiration and heart action, are to be continuously monitored. It is thus essential for correct diagnosis to know the limits of the normal variation of these functions, and also features typical of pathological conditions. This preassumes the use of long-term recordings in research work.

Continuous electrocardiographic and heart rate recordings, without affecting the activities of the subject, are produced in two main ways: 1 using a miniature electrocardiographic transmitter attached to the patient, and a special receiver for detection and reproduction of the signal (radiotelemetric instruments), or 2. employing a small portable electrocardiographic tape recorder connected directly to the patient. A third method, applicable also to these two apparatures, is to conduct the electrocardiographic signal directly to a computer where the information can be processed automatically but this can scarcely be realized in most hospitals at the present time.

The purposes of the present investi gation are to define a suitable and interference-free electrocardiographic tape recording technique for small infants to study peculiarities in the signal reproduction of tape recording equipment; and to determine the alter ation of the heart rate and the electrocardiographic signal postnatally in full-term and premature infants, with long period recordings beginning on the first day of life.

LITERATURE

CONVENTIONAL ELECTROCARDIOGRAPHY IN NEWBORN INFANTS

Full term newborn infant

Paediatric electrocardiography was started by the investigation of Nicolai & Funaro [61] in which a deep S_I deflection, different from the S wave of adults, was found to be a distinctive electrocardiographic feature of small infants. Thereafter an enormous number of studies have been performed the character of which has followed the evolution of electrocardiographic techniques and of modern views of human haemodynamics The electrocardiographic peculiarities of childhood have been designated as a function of age. The transformation of these features appears to be rapid in early infancy particularly during the neonatal period As a result of this, the ECG of the newly born cannot be compared with that recorded days, weeks or months after birth.

Neonatal electrocardiographic findings were described in such publications as Hecht [34] Smith [83] Burghard & Wunnerlich [8] two detailed articles of Nadrai [59 60] that of Battro & Mendy [5] Schaffer et al. [78] Tudbury & Atkinson [92] and Allmurung et al. [2] In the light of these investigations and the monograph Electrocardiographic Studies in Normal Infants and Children by Ziegler [112] it was possible to define the typical features of the neonatal ECG as follows

1 The mean heart rate was 120 to 130 beats per minute, ranging from 90 to 200 beats per minute.

2 The neonatal P waves were found higher than those of older children, and the duration of the P wave became longer after the neonatal period Nadrai showed that the P R interval was prolonged in newborn infants [60]

3 The ventricular depolarization complex indicated right ventricular preponderance, which later in childhood gradually turned into the left ventricular dominance peculiar to adults. A prominent Q wave was often detected in standard leads II and III, and left precordial leads.

4. Inverted T waves were quite common in the precordial electrocardiogram without any evidence of myocardial disease. Also a small S-T deviation up to 0.2 mV was often established in chest leads.

In the investigations published after 1950 contradictory reports concerning neonatal T wave alterations were checked. Both Ziegler [112] and Furman & Halloran [23] divided the neonatal period into smaller segments. In this way it proved possible to clarify *ventricular repolarization* during the first hours, first days and weeks after

birth. According to these later observations the T wave was at first mostly positive in the right precordial chest leads, later becoming inverted [14, 16, 30, 72, 84 86, 107] On the other hand, left precordial T waves were negative immediately after birth and became positive later on. Schaffer et al. noted that the T wave was negative on the right, and positive on the left precordium [76] Also Furman & Halloran detected inverted T_{V1} in more than 50 per cent of newborn infants' there were no negative left precordial T waves in this series [23] Sodi Pallares et al. paid attention to the convex S-T segment, and peaked, asymmetric T wave, peculiar to the neonatal right precordial electrocardiogram [84] Stern & Lind found that the inversion of T_{V1} occurs between the ages of 30 minutes and 6 days [86] This was confirmed by DePasquale & Burch [17]. Scott & Franklin reported that the T wave inversion in the right chest leads occurred during the first week of life [80]. Hait & Gasul showed that the axis of the T wave initially for 0—5 minutes post partum, pointed to the left, then shifted to the right at the age of 1—6 hours, and then once again to the left in a time of seven days. This variation was suspected to be a sign of transient physiologic left ventricular strain [32]

The comparison of electrocardiographic findings with neonatal haemodynamic observations offered new possibilities for explaining T wave alterations. Dupuis et al. demonstrated that changes of T_{V1} coincided with the disappearance of pulmonary hypertension [19] Emmanouilides et al. established a correlation between positive right precordial T waves, high P waves and pulmonary hypertension. There was also a positive correlation between the negative T_{V6} deflections and a neonatal left to-right shunt in ductus arteriosus. R/S ratio in the V6 lead was found to be less than one in cases where the pulmonary arterial pressure was low in relation to the systemic arterial blood pressure [20]

The U deflection was rather rare in the electrocardiogram of newborn infants. Michaëlsson found U waves up to 0.2 mV of magnitude in about one third of infants at the age of one week or less [54] This observation was confirmed by Walsh [107]

The monograph of Wasserburger gave data about normal and abnormal QRS complex morphology in unipolar leads during childhood. This material included a group of 50 infants 0—2 months old, 30 of whom were under 1 week old. Rs and rsR patterns were mostly discovered in the right chest leads and qRs pattern, with a tendency to low voltage and clockwise rotation, was a typical finding of left precordial ECG [110]

Interracial differences in neonatal ECG were described by Sutin & Schrire [90] Right ventricular preponderance was reported as more prominent in white infants than in South-African coloured and Bantu infants.

According to the literature, there seems to be much variation in the values of different conduction phases of neonatal electric cardiac activation. The duration of the P wave ranged from 0.02 to 0.10 s [23, 24, 54, 69 102, 106, 112] the P R time was 0.06—0.14 s [23, 60 72, 102, 106 112] and the *QRS* interval 0.04—0.08 s [23, 24 54, 60, 69 72, 103, 112] The measurements of these intervals were generally performed in standard lead II. DePasquale & Burch stated that the duration of P

CONVENTIONAL ELECTROCARDIO GRAPHY IN NEWBORN INFANTS

Full term newborn infant

Paediatric electrocardiography was started by the investigation of Nicolai & Funaro [61] in which a deep S_I deflection, different from the S wave of adults, was found to be a distinctive electrocardiographic feature of small infants. Thereafter an enormous number of studies have been performed the character of which has followed the evolution of electrocardiographic techniques and of modern views of human haemodynamics. The electrocardiographic peculiarities of childhood have been designated as a function of age The transformation of these features appears to be rapid in early infancy particularly during the neonatal period As a result of this, the ECG of the newly born cannot be compared with that recorded days, weeks or months after birth.

Neonatal electrocardiographic findings were described in such publications as Hecht [34] Smith [83] Burghard & Wunnerlich [8] two detailed articles of Nadrai [59 60] that of Battro & Mendy [5] Schaffer et al. [78] Tudbury & Atkinson [92] and Alimurung et al. [2] In the light of these investigations and the monograph »Electrocardiographic Studies in Normal Infants and Children by Ziegler [112] it was possible to define the typical features of the neonatal ECG as follows

1 The mean heart rate was 120 to 130 beats per minute ranging from 90 to 200 beats per minute.

2 The neonatal P waves were found higher than those of older children, and the duration of the P wave became longer after the neonatal period. Nadrai showed that the P R interval was prolonged in newborn infants [60]

3 The ventricular depolarization complex indicated right ventricular preponderance, which later in childhood gradually turned into the left ventricular dominance peculiar to adults. A prominent Q wave was often detected in standard leads II and III, and left precordial leads

4 Inverted T waves were quite common in the precordial electrocardiogram without any evidence of myocardial disease. Also a small S-T deviation up to 0.2 mV was often established in chest leads

In the investigations published after 1950 contradictory reports concerning neonatal T wave alterations were checked. Both Ziegler [112] and Furman & Halloran [23] divided the neonatal period into smaller segments. In this way it proved possible to clarify *ventricular repolarization during the* first hours first days and weeks after

birth. According to these later observations the T wave was at first mostly positive in the right precordial chest leads, later becoming inverted [14, 16, 30, 72, 84, 86, 107]. On the other hand, left precordial T waves were negative immediately after birth and became positive later on. Schaffer et al. noted that the T wave was negative on the right, and positive on the left precordium [78]. Also Furman & Halloran detected inverted T_{V1} in more than 50 per cent of newborn infants: there were no negative left precordial T waves in this series [23]. Sodi-Pallares et al. paid attention to the convex S-T segment, and peaked, asymmetric T wave, peculiar to the neonatal right precordial electrocardiogram [84]. Stern & Lind found that the inversion of T_{V1} occurs between the ages of 30 minutes and 6 days [86]. This was confirmed by DePasquale & Burch [17]. Scott & Franklin reported that the T wave inversion in the right chest leads occurred during the first week of life [80]. Hait & Gasul showed that the axis of the T wave initially for 0—5 minutes post partum, pointed to the left, then shifted to the right at the age of 1—6 hours, and then once again to the left in a time of seven days. This variation was suspected to be a sign of transient physiologic left ventricular strain [32].

The comparison of electrocardiographic findings with neonatal haemodynamic observations offered new possibilities for explaining T wave alterations. Dupuis et al. demonstrated that changes of T_{V1} coincided with the disappearance of pulmonary hypertension [19]. Emmanouilides et al. established a correlation between positive right precordial T waves, high P waves and pulmonary hypertension. There was also a positive correlation between the negative T_{V5} deflections and a neonatal left-to-right shunt in ductus arteriosus. R/S ratio in the V6 lead was found to be less than one in cases where the pulmonary arterial pressure was low in relation to the systemic arterial blood pressure [20].

The U deflection was rather rare in the electrocardiogram of newborn infants. Michaëlsson found U waves up to 0.2 mV of magnitude in about one third of infants at the age of one week or less [54]. This observation was confirmed by Walsh [107].

The monograph of Wasserburger gave data about normal and abnormal QRS complex morphology in unipolar leads during childhood. This material included a group of 50 infants 0—2 months old, 30 of whom were under 1 week old. Rs and rsR patterns were mostly discovered in the right chest leads and qRs pattern, with a tendency to low voltage and clockwise rotation, was a typical finding of left precordial ECG [110].

Interracial differences in neonatal ECG were described by Sutin & Schrire [90]. Right ventricular preponderance was reported as more prominent in white infants than in South-African coloured and Bantu infants.

According to the literature there seems to be much variation in the values of different conduction phases of neonatal electric cardiac activation. The duration of the P wave ranged from 0.02 to 0.10 s [23, 24, 54, 69, 102, 106, 112], the P-R time was 0.06—0.14 s [23, 60, 72, 102, 106, 112] and the QRS interval 0.04—0.08 s [23, 24, 54, 60, 69, 72, 103, 112]. The measurements of these intervals were generally performed in standard lead II. DePasquale & Burch stated that the duration of P

deflection was constant in the neonatal period [17] The results of Ziegler [112] Walsh [102] and Jagielski et al. [39] indicated a shortening of the P wave duration after birth. The heart rate had no effect on the duration of atrial depolarization. *Generally shorter* P R intervals appear with higher heart rates, but *in newborn infants this* phenomenon is less marked [3] Kessel found that the P R interval was longest 3—5 hours after birth regardless of heart rate [42] Also in the series of *Michaëlsson, the maximal* P R inter vals were noted during the first day of life [54] A gradual decrease of the P R interval in the neonatal period was a common finding [17 39 12, 106] The minimum interval was reached in 1—7 days [112]

The *duration of the* ventricular depolarization complex was minimal during the first 4 weeks of life [23 112] DePasquale & Burch [17] Walsh [103] and Jagielski et al. [39] establish ed the decrease of the QRS duration in their newborn materials. The materials of Nadrai [60] Ziegler [112] Michaëlsson [64] DePasquale & Burch [17] Walsh [103] and Jagielski et al. [39] indicated a transitory prolonga tion of the Q-T interval after birth. Walsh demonstrated that the prolongation of the Q-T interval was mainly due to the prolongation of the duration of the S-T segment [103]

An extreme variation exists between different investigations in respect to the frequency of cardiac rhythm and conduction *disturbances during the* neonatal period. A common characteristic of all these disturbances, however is that they are asymptomatic Some investigators have not mentioned any arrhythmias, although quite large ma terials have been examined. The possi bility of the appearance of a sudden arrhythmia in a short recording is rather small and, on the other hand, mild sinus arrhythmias would not be classifield as true arrhythmias by all authors

The *most frequent* arrhythmia in newborn infants seems to be the sinus *arrhythmia [16 23 30 54, 59 60 68* 92, 112] The highest incidence of respiratory arrythmias (42 %) was reported by Nadrai [59] There are regularly more sinus arrhythmias to be *detected in association with lower heart* rates [112] In most investigations there were only sporadic cases of extrasystole [19 23 54 59 60 72, 83 92] although authors found premature beats in as much as 30 per cent of their material [8] Ventricular extra *systoles proved to be more common* than supraventricular ones.

Single cases of auricular flutter [112] wandering pacemaker [23, 72 104] Wolff Parkinson White syndrome [104] nodal rhythm [19] sinus arrest and supraventricular arrhythmias [54] were discovered in newborn materials. Most of the arrhythmias occurred on the second and third day of life [54] Ziegler described an infant with a grave transitory ventricular conduc*tion disturbance [112] Both Schaffer* et al. [78] and Walsh [104] found one case of right bundle branch block in their materials. There was also one case with a ventricular conduction disturbance in the material of Stern & Lind, which normalized during the observation time [85]

In an impedance pneumographic and electrocardiographic study we found sinus arrhythmia in 60 per cent of the material of 50 newborn infants at ages of up to 10 days. Half of the sinus arrhythmias appared to be connected

with periodical respiration. Although the recording time was very much longer than in ordinary ECG examination, no other arrhythmias were detected [15]

Heart arrythmias in childhood was the theme of the monograph of Landtman [45] No special attention was paid to the neonatal period, but it was mentioned that sinus arrythmia was found, although less pronounced, in the youngest age groups too. Premature beats, auricular flutter and fibrillation, seldom appeared in infants. Two cases of paroxysmal tachycardia, typically occurring in infancy were detected in the neonatal period. Conduction disturbances were also quite rare, only one newborn infant with a complete A V block being described.

Premature newborn infant

According to the early investigations of Noeggerath [62] Hecht [34] Burghard & Wunnerlich [8] Londe [49] Raiha [67], and Nadrai [59 60] it could be concluded that there is no neonatal electrocardiogram peculiar to premature babies, although some features differ from that of full-term newborn infants

— low voltage in QRS complex was more common in premature material, especially in the group with a small birth weight,

— P and T waves were also of lower amplitude and could even be lacking,

— the premature generally had higher heart rates,

— less respiratory sinus arrythmia was found among prematures, but real rhythm irregularities were quite frequent [67].

A contrary result was expressed by Landtman, where many arrythmias, though not sinus arrythmia, were rarely found in premature infants [45] The reason for this discrepancy may be the longer ECG recording time employed by Räihä [67]

More information about the ECG of the premature newborn infants was obtained using precordial leads [38, 47 74, 75 76 87 101] Less prominent right axis deviation was found in premature babies than in full-term material, and deep Q waves were common in the left precordial leads. The right precordial T waves appeared to be often negative during the first day of life, which was believed to be a sign of a less marked right ventricular strain than in infants delivered at term. It was suggested by Stoermer that the persistence of positive right precordial T waves indicated abnormal right ventricular hypertrophy [87] A shift of the negative T wave to the left was a common finding in the series of Thaon [91] Stoermer [87] and Salmi et al. [76] The left precordial T waves were mostly positive during the first day the same was the case after the second day of life. Thus the behaviour of neonatal T deflections in the left precordial ECG in premature infants resembled that of full-term babies. The P R interval was a little shorter in the premature compared with the values of the full-term neonates, but also prolonged atrio-ventricular conduction was to be detected [74, 75, 91] The prematures had QRS intervals of the same, or smaller magnitude as the full-term infants [75 87 91]

A profound longitudinal study concerning the evolution of the ECG of premature infants during the first year of life was published by Walsh [105] According to this work the variation

of heart rate was 100—200/min. The mean heart rate was higher than in full term infants. One case with an abnormal bradycardia of 65 beats per minute was mentioned. Premature babies with a birth weight less than 1500 g tended to have faster heart rates, especially at the age of one to three months. Arrhytmias were quite uncom mon in this series. The P wave dura tion, P R interval and QRS interval increased during the first year of life The Q-T index had a minimum at one to three months. The right precordial P waves were often peaked or diphasic during the first week of life. This phenomenon had been observed earlier and was suspected to represent a sign of right atrial overload [76 91 101 111] 75 % of the material had a right axis deviation and 6 % had a left axis deviation at birth [105] T deflections were well defined but low in the chest leads, while the observations concerning the direction of T waves were in argeement with earlier investiga tions U waves were discovered in about one third of the material at some time during the period observed. They were mostly found in the right precor dial ECG

Peaked P waves and a low QRS voltage were also reported by Fonseca Costa et al. [22] These authors found a relationship between the greater occurrence of Q_{V1}, negative right precordial T waves, and lower birth weight. This was considered to be a sign of a greater degree of immaturity The higher P waves, shorter intervals of cardiac activation, and lower voltage of the ECG of premature infants were confirmed by Berlinerblau [7] and it could be concluded that no clear electrocardiographic signs typical of premature infants could be defined

CONTINUOUS ELECTROGARDIOGRAPHY

Conventional electrocardiographs have some disadvantages for special purposes. Long term recordings are un comfortable for the subject, because he is connected to the instrument and thus unable to perform normal activities. On the other hand these cardiac changes during every-day work are the most important criteria for the diagnosis and the degree of invalidity of a spesific heart disease. Another problem is the adequate analysis of a long period segment of electrocardiogram consisting of thousands of signals with almost equal configuration. The length of a roll of a conventional electrocardiograph paper is also a limit for record ings lasting hours or days.

All the problems mentioned above were resolved technically by a small portable electrocardiographic tape recorder (Electrocardiocorder) and the rapid analysing equipment (AVSEP Audio-Visual Superimposed Electrocar diographic Presentation) of Holter in 1961 [36] These instruments, manu factured commercially by Avionics Research Products Corporation, Los Angeles, California, will be described more thoroughly in section 1 of this investigation.

Observations concerning the clinical use of Holter's tape recording system were published by Gilson et al. [27] Attention was paid to reducing the inaccuracy of the recording by improv ing recording technique Comparisons were made between the electrocardiographic configuration in unipolar and bipolar chest leads, and also between the fidelity characteristics of a conventional electrocardiograph and those of Holter's instruments. It was concluded

that differing electrode placements produced very similar patterns in both chest leads studied, and thus the bipolar lead CSR-C5 was accepted for continuous recording. The oscilloscopic presentation in AVSEP differed from the pattern produced with the conventional machine. These differences included deeper S waves, slight deviations of S-T segment and deformations of T wave (socalled «pre-T notch» and «post T dip»). Basic electrocardiographic patterns of healthy adults were presented. The P wave and QRS complex were found to be quite stable, whereas the S-T T segment showed both dynamic and individual variations. Some features of the most common arrhythmias were presented, and difficulties in their identification were discussed. Stress was also laid on the importance of experience in excluding artifacts produced by the system itself.

Both Norland & Semler [63] and Corday et al. [13] used Holter's instruments to examine a large number of patients, mainly adults, among whom they picked up case reports concerning evanescent cardiac arrhythmias and stenocardiac attacks. Descriptions of the use of the tape recording method including case reports were published also by Arstila et al [4], Roskamm et al. [71], Matzdorff & Schmidt [51] and Shumak & Brown [81]. Gilson et al. [26] described 4 cases with unusual QRS alterations among a material of 400 recordings. Gilson [25] published a longitudinal study of AVSEP-patterns recorded in adult men during four years. It was found that a similar basic pattern was recorded every year in 81 per cent of the cases. Alterations were detected mostly in repolarization deflections. Arrhythmias were surprisingly rare. Sanders & Martt [77] reported observations of the use of electrocardiocording at high altitude.

The advantages and limitations of Holter's method were discussed on the basis of carefully standardized recordings performed in a large group of active adult men [35]. The characteristics of several Electrocardiocorders of different type series were compared. The speed constancy and cumulative timing error of the new Model 350 C series were found to be better than those of the older Model 350 C. Also a small time non-linearity in the scanner time-base was detected. A marked decay at the end of a test square wave was observed both in the scanner and charter outputs. The final ECG writer of the charter was not responsible for this phenomenon. The over-all frequency response was confirmed to be practically equal with that specified by the manufacturer. These results indicated that some distortion, especially in the low-frequency components, i.e. S—T—T region, of the ECG is to be expected. This fact was also confirmed by studying the configuration of an ECG test signal. There were often difficulties in identifying S—T deviations and arrhythmias with the scanning technique. It was concluded that the interpretation of changes particularly affected by the electronic peculiarities of the instruments, e.g. S—T deviations and T wave abnormalities, can lead to false results, when the limitations of the method are not understood. For a more accurate analysis of recordings a photographic write-out of R—R intervals with real-time scanning, and a careful examination of all potential segments of abnormality was recommended.

Short case reports of arrhythmias, e.g. conversion of paroxysmal tachycardias

to sinus rhythm, A V blocks of different degrees, and ectopic pacemakers in childhood, studied with Holter's appa ratture, were published by Morgan et al. [56] and Välimäki [96] The former investigation included an example of processing the tape through a computer to obtain a histogram of R—R intervals.

CONTINUOUS ELECTROCARDIO GRAPHY IN NEWBORN INFANTS

In 1965 Morgan and Guntheroth published data obtained from 50 newborn infants at the age of one hour to 7 days by means of Holter's apparature [57] Standard lead I was used and recordings were taken for 3 1/2 to 5 hours. Primary attention was directed *to the cardiac rhythm. Sinus arrhythmia* was observed in all infants. The heart rate varied from 70 to 180 per minute. Occasional premature beats were found in a few infants. One case of incomplete atrioventricular block was also mentioned Thus quite a normal cardiac mechanism was usually found in full term babies

The case was otherwise with premature newborn infants, according to the earlier report of Morgan et al. [55] The series consisted of 20 infants at ages from 5 hours to 29 days. A marked sinus bradycardia was observed in 8 cases and 5 additional infants had sinus bradycardia with nodal escape. One infant had a first degree A V block Sinus bradycardia was more common in the lower birth weight groups. The effect of digitalization and the vegetative tonus of premature infants were discussed on the basis of these results.

Our team also introduced two case reports of newborn babies, one with vegetative T wave changes after crying and the other with 2 1 A V block, which was transformed first to sinus rhythm, then to a bizarre ventricular conduction pattern, and later once again to sinus rhythm with S—T deviation [4] Preliminary reports of the present investigation were published in abstract form [95 97]

PRESENT INVESTIGATION

SECTION I DEVELOPMENT OF METHODOLOGY

THE EQUIPMENT OF HOLTER-AVIONICS

The frequency components of human electrocardiographic signals include too low frequencies to be directly utilized in electronic apparatuses. Thus higher frequency carrier wave, modified (frequency modulated) by the cardiogenic signal, is employed in units that allow long segments of ECG to be recorded on a magnetic tape. For this procedure, large, complicated, and expensive devices are required.

Full freedom in transportability of the recorder and relative simplicity of the analyser unit were gained, at the same time avoiding the frequency modulation, in the electrocardiographic tape recording method introduced by Holter [36]. The apparature of this method consists of a small, battery powered recorder (Electrocardiocorder ®), a rapid analyser (Electrocardioscanner ®), and writer unit (Electrocardiocharter TM).

Electrocardiocorder

Electrocardiocorder Model 150 is a miniature twochannel recorder weighing 1350 g, designed to be carried by the subject. The tape speed is exceptionally slow only 0,21 cm. The frequency response of the machine is 0,1—100 cps. The ECG signal is simultaneously recorded on two tracks of the tape by the two channels of the device. One is the actual ECG pattern channel by which the ECG is amplified, and, mixed with bias alternating current, recorded on the tape in the pattern recording head. The other is a trigger channel by which the ECG pulse is transformed into sharp trigger pulse. The trigger head is located at some distance from the pattern head, which enables slightly earlier recording of the trigger signal on the tape. The purpose of this arrangement is that the trigger signal will trigger the sweep of the »pattern» display of the Electrocardioscanner and the QRS complex of the synchronous pattern recording will be placed in the middle of the sweep. Small reels of magnetic tape provide a recording of 6 to 18 hours, depending on the thickness of the tape. The capacity of the power supply a small nickelcadmium battery restricts the continuous recording time to 10 hours. The original electrodes and cords are for bipolar leads. A marking and calibration deflection of 1 mV may be recorded on the tape by pushing a calibration button in the operating panel of the Electrocardiocorder. A repetitive one-millivolt pulse, with frequency of 1 cps, can be obtained by means of the One-Milli volt Calibrator (Avionics) in order to calibrate the scanner unit.

Electrocardioscanner

The recording is analysed at a 60 times accelerated tape speed in the Electrocardioscanner Model 430. Thus a band width of 6—6000 cps is reached, and the ECG potentials can be reproduced without frequency modulation. The accelerated play back technique also enables the rapid analysis of a long recording. The ECG pattern signal is applied through an amplifier to the »ECG-pattern» oscilloscope (AVSEPs) of the scanner. The trigger signal is utilized to adjust the length of the sweep of the oscilloscope equal with the R—R interval. This produces a superimposed presentation of successive ECG complexes on the screen.

Thus sudden changes in the ECG are easily detected as a movielike alteration of the PQRST configuration.

A saw tooth voltage proportioned to the recorded R—R intervals, is fed to the other oscilloscope (Arrhythmiagraph) of the scanner unit to indicate the variation of the heart rate, which is also to be heard as a steady growl through a loud speak er This AVSEP technique enables the examiner to concentrate on following the ECG pattern on the screen, while the heart rate can be heard at the same time. Phenomena recorded on the tape can be timed by comparing the diary notes of the Electrocardiocorder examination and the time reading in a small clock of the scanner which is mechanically turned by the tape Both oscilloscopes are to be calibrated in dependently with the one-millivolt rectangular pulse. This pulse is a reference for both voltage and timebase calibration.

Electrocardiocharter

If electrocardiographic abnormalities are detected during the play back procedure in the scanner these can be written out by means of the third unit, Electrocardiocharter Model 550. The original recording is placed on the operating deck of the machine where the tape speed is once again the original 0.31 cm/s. The movement of the recording can be followed with a real time clock similar to that of the scanner Because of the slow tape speed, the gap of the reproducing head of the charter must be unusually wide to detect the slowly changing magnetic field. The signal is amplifield and fed to the input of an oscillograph (Burdick EK III Electrocardiograph) to be printed on a conventional ECG paper

The operation demands (small size, porta bility signal reproduction of good quality simple construction) of the Electrocardiocorder AVSEP instruments have led to some technical compromises in the manufacturing of these devices. The stability of the baseline is achieved by restricting the low frequency response, which leads to some insufficiency in repeating some essential frequency components of the ECG It has been stressed that findings obtained with this method are not comparable to those of conventional electrocardiography [27 35] Although a considerable non-linearity of the frequency response already exists in the recorder stage, additional distortion is evidently produced by the charter procedure. To avoid these distortions an additional method has been developed for printing the recorded tape information on ECG paper

MV 1 METHOD

This method was designed for a cardiological laboratory in which there is regular ECG equipment, e.g. electrocardiographs and oscilloscopes available, and thus only two additional components, a tape recorder of high quality and a special FM-modulator demodulator MV 1 are needed. This last has been developed and tested in the electronic laboratory of Lääketukku Oy Helsinki, Finland, and in the Cardiorespira tory Research Unit of the University of Turku. The MV 1 unit itself was con structed by an engineer T Åhman (Lääketukku Oy) Preliminary reports concerning this method have been published previously [50 113]

According to this method, the original Electrocardiocorder recording is analysed in the Electrocardioscanner and during the play back procedure the ECG signal is taken from the ECG output of the scanner to the MV 1 unit. In this unit the signal is frequency modulated and amplified, and then transferred for a re-recording to a regular high fidelity tape recorder For this purpose we have used an Akai M-8 tape recorder (Akai Electric Co. Ltd., Tokyo), which has the frequency response of 30—25 000 cps. The tape speed of the re-recording is 38,1 cm/s. After the diagnostic portion of the original recording has been re-recorded, the re-recording is played at the tape speed of 4,76 cm/s and the signal is fed back to the MV 1 where it is amplified and demodulated and transferred to a conventional electrocardiograph (Mingograph 34, Elema, Stockholm) to be printed on paper The whole of this procedure is essential, because normal oscillographs are not able to write all the fre-

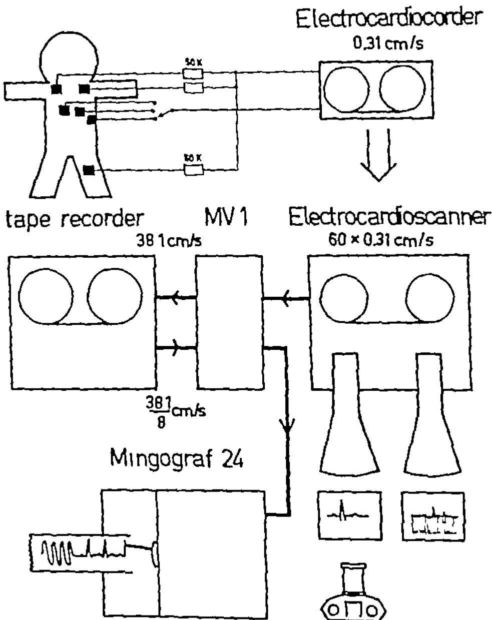


Fig 1 Block diagram of the tape recording and analyzing procedures f ECG with Electrocardiocorder and Electrocardioscanner — MV 1 — Akai M-8 tape recorder — Mingograf 24 chain.

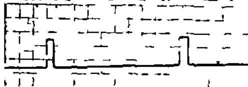
quencies of 6—60 000 cps produced by the Electrocardioscanner As the tape speed of re-recording is reduced to 1/8, a frequency range of 0.75—750 cps is reached. Most rapid oscillographs are able to repeat these frequencies without noteworthy non-linearity The frequency modulation enables better signal reproduction, in fact there are no restrictions with regard to the representation of lower frequencies. An additional oscilloscope is connected to the DC-amplifier of the Mingograph. Thus the ECG pattern of the re-recording is visualised, and the heart rate is to be heard in

the loudspeaker of the Akai tape recorder Once again an audio-visual presentation is utilised, and this facilitates the detection of *momentary alterations of* the recorded ECG For this oscilloscopic display the Atlas 46 A oscilloscope (Atlas Werke A. G Bremen) has been used.

The block diagram of the electrocardi ocording and analysing procedures is presented in Fig. 1 The recordings of one-millivolt rectangular calibration pulse made with Mingograph 24 and the Electrocardiocorder the latter recording written out by means of the Electrocardiocharter and the MV 1 link, are compared in Fig. 2. We have tested the responses of both the scanner unit and the MV 1 link, by making an Electrocardiocorder recording with a sine wave pulse generator The voltage losses detected in the middle of the frequency range of the scanner ECG output being compensated in the construction of MV 1 amplifier

In practice the Electrocardiocharter is throublesome to use, because the original recording must be removed from the deck of the scanner to that of the charter and the interesting point of the recording can thus be lost. The detecting of such a point can be difficult without an oscilloscope control, and involves the expense of much time and ECG paper In the MV 1 system the final signal can be continuously followed with an oscilloscope and a loudspeaker and only the essential segments need to be printed on paper The original recording can stay on the scanner deck all the time. These practical difficulties have been par tially eliminated in the Composite Electrocardioscanner Model 651 of Avionics, which includes both the scanner and the charter units.

MINGOGRAF 24



ECCHARTER



MV-1



ECSCANNER

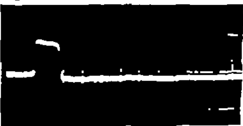


Fig. 2. Mingograf 24, Electrocardiocharter MV 1 and Electrocardioscanner reproductions of the 1 mV/1 cps calibration pulse of One-Millivolt Calibrator

ADJUSTMENTS OF THE APPARATURE FOR THE PRESENT STUDY

Recording

The AVSEP scanner *analysis* presumes an undisturbed tape recording of the ECG signal. Three major disturbing factors must be eliminated 1) the alternatig current noise, 2) the muscle potentials and 3) the wandering of the base line These factors become particularly important when we have an unco-operative subject like a new born infant, when we must continue our

recording for hours or days, mostly without oscilloscope control, and when we should like to get electrocardiographic information even during irritation, crying, and movements

In the present investigation, the occurrence of the local alternating currents in the rooms of hospital wards was determined by utilizing a special antenna loop connected to an electrocardiograph. The place with a minimal inducting alternating current was chosen for recording A Faraday cage was placed on the bed or incubator of the infant. The connecting wires, of minimal length, were supplied with a metal mantle outside the Faraday cage. The cage bed, mantle and the case of the recorder were earthed with a single wire. Earthing of the patient was not needed.

Muscle potentials are not a very grave problem, because they are to be seen as small irregular vanishing serrations of the base line during the scanner analysis. The only way to avoid them completely is to place the electrodes far from muscles, and this is sometimes impossible. In this study the electrodes of the central terminal were placed on the subclavicular areas and on the proximal left thigh, an arrangement which also reduced the base line shift. Although this proximal central terminal placement causes a minor reduction of the QRS voltage, this difference is not statistically significant [98]

The proper attachment of the electrodes is essential for minimising the base line movement, and producing an electrode-skin resistance suitably low for equipment applied. Various standard electrodes and electrode jellies were tried. Finally our own miniature electrodes were constructed, which consisted of a 1.2 × 1.2 cm brass net screen connected to the wire by means of a snap fastener Since the wire had to be exceedingly flexible, it was made of a hearing aid wire in which the conducting metal tape was wrapped around a cotton. The best electrode jelly proved to be Trucon Electrode Paste (Electrodyne, Westwood, Massachusetts) The skin was cleaned with alcohol solution, rubbed until a mild erythema appeared, and the electrode provided with jelly was attached to it with 3M N:o 1525 Blenderm Tape. Both the jelly and the adhesive tape were well tolerated during a period of 20—30 hours.

Three chest leads, V1 V3 and V5 were recorded successively These leads were chosen not only because of the high signal to-noise ratio but also because there is a lot of information about results obtained with chest leads by conventional electrocardiography This enables conclusions concerning the position of the cardiac electric axis to be drawn from results recorded with these three leads, and finally because the lead system is not too difficult to attach quickly Resistors of 50 kΩ were connected in the classical manner to the central terminal. A lead selector constructed in our laboratory made the changing of leads possible.

The Electrocardiocorder Model 350 A was used for recording. The original battery of Avionics was replaced by a larger NiFe-accumulator which was connected to the recorder with an earthed wire and an extra plug in jack. This provided power enough for recordings of more than 100 hours without charging. Permatone TX-S-8 magnetic tape was used for registration, the small reels suitable for the recorder being sufficient for 14-hour recordings.

Analysing procedures

The recordings obtained were scrutinised with the Electrocardioscanner Model 450 The AVSEP display of the machine was calibrated by means of 1 mV/1 cps and 1 mV/2 cps calibration pulse recordings, adjusting 1 mV equal to 10 mm and 0.5 s equal to 50 mm on the screen. The higher heart rate scale was utilised on the Arrhythmia graph, which was calibrated according to the 1 mV/1 cps recording

The ECG configuration was examined directly by measuring the time and voltage quantities on the screen and when necessary the pattern was photographed with an Exa camera (Ihagee, Dresden) on Kodak Tri X film with a close-up time of 1/25 s. The comparison of the values obtained directly and those measured on the exposures showed that sufficient accuracy was achieved by measuring the quantities directly 0.5 mm was the minimum unit in these measurements.

Suddenly appearing electrocardiographic alterations (e g rhythm irregularities, S-T and T alterations) were photographed on the AVSEP oscilloscope This is not very often elucidating because a large group of electrocardiographic complexes are superimposed on the AVSEP screen during the rapid play back. Therefore the interesting portions of the recording were written out on paper mainly by means of the MV 1 method. For calibration and comparison, the 1 mV/1 cps pulse and the beginning pattern of each recording were registered on paper by the MV 1 technique when the scanner analysis was started. The occurrence of sudden rapid phenomena was carefully timed by the aid of the clock mechanism and the diary

The Electrocardiocharter was not used regularly in this study for printing the recorded ECG on paper To secure as much information as possible from the presentation of the recorded ECG most of the sudden irregularities were also written out using either the Electrocardiocharter 550 of the Cardiologic Laboratory of the Meilahti Clinics of the University Central Hospital of Helsinki Finland, or the new Composite Electrocardioscanner 651 of our own clinic. The results obtained with different analysing techniques are somewhat different, and therefore data and comments are presented in the following chapters concerning the peculiarities, advantages, and limitations of the methodology used.

TECHNICAL OBSERVATIONS

Calibration

The commercial equipment is designed mainly for adults, and therefore the rate of the basal calibration pulse, produced by the One-Millivolt Calibrator is 1 cps This test pulse is of good quality in the conventional recordings as can be seen in Fig 2, where also the distortion of this pulse in the scanner charter and MV 1 reproductions is demonstrated. The originally rectangular pulse becomes deformed in the scanner so that there is a small spike of 0 1 mV in the rising loop and a droop of similar magnitude in the descending loop These artifacts are more marked in the newer models of Electrocardioscanner Electrocardiocharter and Composite Electrocardioscanner than in the apparatus mainly employed in this study On the other hand, some damp-

ing takes place in the MV 1 link, the pulse becoming rounded in the final presentation.

Besides the standard pulse of 1 cps, another higher calibration frequency is useful when heart rates of small infants are studied. In the present investi gation the scanner unit was also cali brated by means of a tape recording of a pulse with frequency of 2 cps, which gives a rate of 120/min, a typical heart rate of newborn infants.

It is unpractical to record the cali bration pulse in the middle of a long ECG recording. Thus, in contrast to conventional electrocardiography the voltage response of the whole tape can not be checked. Therefore a defective and nonquantitatively magnetized tape segment can be responsible for sudden voltage drops, towards which a reserved attitude must be taken.

Timing error

The clock of the scanner (and charter), is moved mechanically by the tape which turns a small pulley on the deck of the machine. Thus, the exactness of the clock depends upon the friction between the tape and the pulley. Also the properties of the reels, brakes, capstans, and pinch rollers, both in the recorder and analysers, cause some timing errors. These have been studied by Hinkle et al. [35] and a cumula tive timing error of +14 to —8 per cent has been presented fo Model A recorders. This error is not a constant one during the course of the recording. Our equipment gave an error up to + 12 per cent at the beginning, which diminished to zero to the end of the ecording, when Permatone TX-S-8 tape was used. We took off the spin from the take-up reel axis: thus there was friction between the axis and the reel, instead of the axis and the rubber loop of the tape transport mechanism. The traction effect of the take-up reel was diminished, and a better time stability of the tape transport was produced. The timing errors could be corrected by means of a regular marking e.g. lead changing, and exact diary keeping.

Base line error

The base line of the scanner oscilloscope is not a straight one as can be seen in Fig. 3. There is a disturbing sine wave of low amplitude present even in the first amplification stage and this must be kept in mind when analysing S-T and T alterations. This distorted base line may be partially responsible for the pre-T notch, an artifact found in one half of the tape recordings studied by Gilson et al. [27]. It does not disturb the analysis, if the duration of S-T segment is not the subject of measurements. The sine wave of the base line is somewhat amplified in the MV 1 presentation. We have not tried to correct this disturbing factor because it seems to be a construction peculiarity in all the equipment we have used.

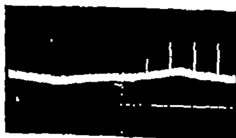


Fig. 3. The deformed base line of the AVSEP display of Electrocardioscanner: the 60 cps calibration pulse of the scanner amplified with maximal vertical gain.

Analysing procedures

The recordings obtained were scru tinised with the Electrocardioscanner Model 450 The AVSEP display of the machine was calibrated by means of 1 mV/1 cps and 1 mV/2 cps calibration pulse recordings adjusting 1 mV equal to 10 mm, and 0.5 s equal to 50 mm on the screen. The higher heart rate scale was utilised on the Arrhythmia graph, which was calibrated according to the 1 mV/1 cps recording

The ECG configuration was examined directly by measuring the time and voltage quantities on the screen and when necessary the pattern was photographed with an Exa camera (Ihagee Dresden) on Kodak Tri X film with a close-up time of 1/25 s. The comparison of the values obtained directly and those measured on the exposures showed that sufficient accuracy was achieved by measuring the quantities directly 0.5 mm was the minimum unit in these measurements.

Suddenly appearing electrocardiographic alterations (e.g rhythm irreg ularities, S-T and T alterations) were photographed on the AVSEP oscilloscope. This is not very often elucidating, because a large group of electrocardiographic complexes are superimposed on the AVSEP screen during the rapid play back. Therefore the interesting portions of the recording were written out on paper mainly by means of the MV 1 method. For calibration and comparison, the 1 mV/1 cps pulse and the beginning pattern of each recording were registered on paper by the MV 1 technique, when the scanner analysis was started. The occurrence of sudden rapid phenomena was carefully timed by the aid of the clock mechanism and the diary

The Electrocardiocharter was not used regularly in this study for printing the recorded ECG on paper To secure as much information as possible from the presentation of the recorded ECG most of the sudden irregularities were also written out using either the Electrocardiocharter 550 of the Cardiologic Laboratory of the *Meilahti Clinics* of the University Central Hospital of Hel sinki Finland or the new Composite Electrocardioscanner 651 of our own clinic. The results obtained with dif ferent analysing techniques are somewhat different, and therefore data and comments are presented in the follow ing chapters concerning the peculiari ties advantages, and limitations of the methodology used.

TECHNICAL OBSERVATIONS

Calibration

The commercial equipment is designed mainly for adults, and therefore the rate of the basal calibration pulse, produced by the *One-Millivolt Calibrator* is 1 cps This test pulse is of good quality in the conventional recordings as can be seen in Fig 2, where also the distortion of this pulse in the scan ner charter and MV 1 reproductions is demonstrated. The originally rec tangular pulse becomes deformed in the scanner so that there is a small spike of 0 1 mV in the rising loop, and a droop of similar magnitude in the descending loop These artifacts are more marked in the newer models of Electrocardioscanner Electrocardiocharter and Com posite Electrocardioscanner than in the apparatus mainly employed in this study On the other hand, some damp-

ing takes place in the MV 1 link, the pulse becoming rounded in the final presentation.

Besides the standard pulse of 1 cps, another higher calibration frequency is useful when heart rates of small infants are studied. In the present investigation the scanner unit was also calibrated by means of a tape recording of a pulse with frequency of 2 cps, which gives a rate of 120/min, a typical heart rate of newborn infants.

It is unpractical to record the calibration pulse in the middle of a long ECG recording. Thus, in contrast to conventional electrocardiography the voltage response of the whole tape cannot be checked. Therefore a defective and nonquantitatively magnetized tape segment can be responsible for sudden voltage drops, towards which a reserved attitude must be taken.

Timing error

The clock of the scanner (and charter) is moved mechanically by the tape, which turns a small pulley on the deck of the machine. Thus, the exactness of the clock depends upon the friction between the tape and the pulley. Also the properties of the reels, brakes, capstans, and pinch rollers, both in the recorder and analysers, cause some timing errors. These have been studied by Hinkle et al. [35] and a cumulative timing error of +14 to —8 per cent has been presented for Model A recorders. This error is not a constant one during the course of the recording. Our equipment gave an error up to + 12 per cent t the beginning, which diminished to zero to the end of the recording, when Permatone TX S-8 tape was used. We took off the spin from the take-up reel axis: thus there was friction between the axis and the reel, instead of the axis and the rubber loop of the tape transport mechanism. The traction effect of the take-up reel was diminished, and a better time stability of the tape transport was produced. The timing errors could be corrected by means of a regular marking, e.g. lead changing and exact diary keeping.

Base line error

The base line of the scanner oscilloscope is not a straight one as can be seen in Fig. 1. There is a disturbing sine wave of low amplitude present even in the first amplification stage, and this must be kept in mind when analysing S-T and T alterations. This distorted base line may be partially responsible for the pre-T notch, an artifact found in one half of the tape recordings studied by Gilson et al. [27]. It does not disturb the analysis, if the duration of S-T segment is not the subject of measurements. The sine wave of the base line is somewhat amplified in the MV 1 presentation. We have not tried to correct this disturbing factor because it seems to be a construction peculiarity in all the equipment we have used.



Fig. 1. The deformed base line of the AVSEP display of Electrocardioscanner: the 50 cps calibration pulse of the scanner amplified with maximal vertical gain.

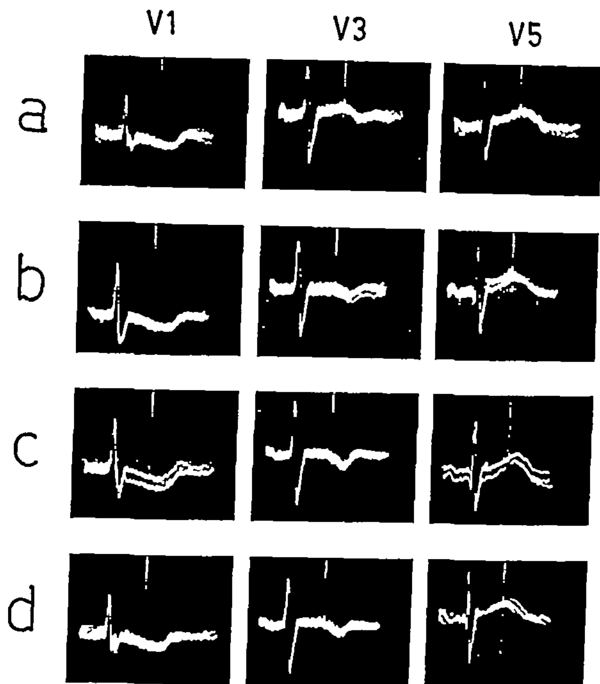


Fig. 4. Effect of posture on ECG tape recording in 6 days old premature male. Electrocardioscanner reproductions of recording performed in a) supine b) right lateral, c) prone and d) left lateral positions.

Effect of postural changes on the ECG

This effect has been noted previously e.g Holzmann [37]. Changes resulting from the movement between exploring electrodes and the skin, and/or the heart, are demonstrated in the tape recordings of Fig 4. To eliminate these postural artifacts all the recordings were performed in supine position. Because of the long recording time, the infants, especially the premature ones treated in incubators, could change their posture which must be kept in mind when analysing the tapes.

Effect of electrode impedance

A skin-to-electrode impedance of 2—20 kΩ was achieved by the careful skin preparing procedure and electrode attachment described above. The higher values were obtained at the beginning of the recording. This is of the same magnitude described for lead-Nobecutane ®— gauze electrodes by Gilson & Grifling [26]. The recommendation of the American Heart Association gives an upper limit of 5 kΩ for electrode impedance in directwriting electrocardiographs [11], but the maximal optimal impedance of Holter's device has been mentioned to be 20 kΩ [76].

COMPARISON OF CONVENTIONAL AND TAPE RECORDINGS

Examples of the ECG patterns reproduced by conventional devices and the tape recording devices of Holter were described by Gilson et al. [27]. A conventionally recorded ECG in V5 and C5R—C5 leads, was compared with that recorded in C5R—C5 lead by Holter's technique. The differences between conventional and tape recording patterns were supposed to be due to the electronic characteristics of these two kinds of recording machines. Exact data, concerning the comparability of the ECG configuration recorded by means of Holter's apparature with the pattern obtained by conventional technique in the same electrode placement, are not available.

To elucidate this problem, a series of 30 healthy full term infants, 15 boys and 15 girls, were examined at the Obstetric Department of the District Hospital of Lohmaa. None of the babies showed any signs of cardiac anomaly in a careful physical examination. The average birth weight of the material was 3450 g and the average age was 3 /2 days. Three chest leads, V1, V3 and V5 with a proximally placed central terminal were recorded with the subject sleeping or resting in supine position in the manner described previously in this section (page 18). With the same electrode attachment, recordings were carried out by means of a conventional Mingograph 24 electrocardiograph (Elema, Stockholm) and thereafter with Electrocardiocorder 350 A (Avionics, Los Angeles). The calibration of the conventional ECG was 1 mV equal to 10 mm, that of the tape recording was produced by the One-Millivolt-Calibrator. The paper speed in the Mingograph was 25 mm/s, the recording time lasting approximately 5 s. Each tape recording included 10 minute segments for each of the three leads.

The durations of P, P—R interval and QRS, and the amplitudes of P, Q, R, S, S—T deviation, T and U deflections were measured in the conventional recordings. The tapes were analysed in the way explained in »analyzing procedures» (page 20). The data mentioned above were directly measured on the ECG oscilloscope of the scanner during the play-back. The analysis was performed by means of both Electrocardioscanner Model 450 and Composite Electrocardioscanner Model 651. The former was coupled to the MV 1 link, the latter includes the charter unit. The determinations of the electrocardiographic quantities were also made in the MV 1 and charter reproductions.

The data were punched on cards and the information was processed in an IBM 1130 computer. The data of the

Table I. Amplitudes of P, R, S and T waves, and S-T deviations (mV) in 30 conventional and tape recording reproductions of V1, V3, and V5.

P wave (positive deflection)

Reproduction	V1 mean	V1 S.D	V1 range	V3 mean	V3 S.D	V3 range	V5 mean	V5 S.D	V5 range
ECScanner 450	0.07	0.04	0.20 — 0.02	0.09	0.05	0.20 — 0.03	0.07	0.04	0.20 — 0.02
Mingograf 24	0.08	0.08	0.30 — 0.02	0.11	0.08	0.25 — 0.03	0.08	0.06	0.30 — 0.03
ECScanner } 651	0.07	0.04	0.20 — 0.01	0.09	0.05	0.20 — 0.03	0.07	0.05	0.25 — 0.02
ECCharter } 651	0.07	0.04	0.20 — 0.02	0.08	0.04	0.20 — 0.03	0.08	0.04	0.15 — 0.02
MV 1	0.08	0.05	0.22 — 0.02	0.10	0.08	0.25 — 0.05	0.06	0.04	0.20 — 0.03

R wave

Reproduction	V1 mean	V1 S.D	V1 range	V3 mean	V3 S.D	V3 range	V5 mean	V5 S.D	V5 range
ECScanner 450	1.12	0.41	1.90 — 0.60	1.39	0.35	2.00 — 0.50	0.89	0.37	1.60 — 0.30
Mingograf 24	1.20	0.45	2.15 — 0.65	1.70	0.51	2.80 — 0.70*	1.04	0.47	2.00 — 0.35
ECScanner } 651	1.08	0.41	1.80 — 0.50	1.34	0.34	1.90 — 0.45	0.87	0.38	1.60 — 0.30
ECCharter } 651	1.04	0.42	1.90 — 0.50	1.28	0.36	2.00 — 0.40	0.83	0.38	1.65 — 0.25
MV 1	0.97	0.38	2.00 — 0.44	1.18	0.29	1.80 — 0.44**	0.75	0.32	1.33 — 0.25

S wave

Reproduction	V1 mean	V1 S.D	V1 range	V3 mean	V3 S.D	V3 range	V5 mean	V5 S.D	V5 range
ECScanner 450	0.57	0.25	1.00 — 0.10	0.94	0.20	1.50 — 0.60	0.77	0.20	1.20 — 0.30
Mingograf 24	0.78	0.54	2.60 — 0.10*	1.58	0.52	2.90 — 0.85**	1.19	0.49	2.40 — 0.20**
ECScanner } 651	0.61	0.28	1.10 — 0.10	0.96	0.19	1.40 — 0.60	0.81	0.19	1.20 — 0.40
ECCharter } 651	0.49	0.23	0.90 — 0.05	0.88	0.27	1.60 — 0.50	0.84	0.20	1.00 — 0.25**
MV 1	0.49	0.25	1.00 — 0.05	0.83	0.24	1.25 — 0.45	0.65	0.25	1.16 — 0.17*

T wave (main or initial deflection)

ECScanner 450	−0.11	0.15	0.30 — −0.45	−0.06	0.17	0.25 — −0.30	0.12	0.11	0.30 — −0.30
Mingograf 24	−0.12	0.21	0.40 — −0.58	−0.11	0.19	0.25 — −0.58	0.14	0.14	0.50 — −0.30
ECScanner } 651	−0.12	0.17	0.20 — −0.45	−0.08	0.14	0.25 — −0.30	0.12	0.12	0.30 — −0.35
ECCharter } 651	−0.12	0.17	0.20 — −0.50	−0.08	0.15	0.20 — −0.40	0.11	0.13	0.30 — −0.35
MV 1	−0.13	0.21	0.25 — −0.50	−0.12	0.19	0.25 — −0.50	0.12	0.15	0.45 — −0.25

Deviation of S–T segment

ECScanner 450	−0.02	0.03	0.00 — −0.10	−0.003	0.01	0.00 — −0.05	0.04	0.05	0.15 — 0.00
Mingograf 24	−0.05	0.05	0.00 — −0.25	−0.02	0.06	0.10 — −0.20	0.03	0.05	0.20 — −0.05
ECScanner } 651	−0.02	0.03	0.00 — −0.10	−0.01	0.03	0.00 — −0.10*	0.04	0.05	0.20 — 0.00
ECCharter } 651	−0.03	0.05	0.00 — −0.20	−0.005	0.02	0.00 — −0.05	0.04	0.05	0.20 — 0.00
MV 1	−0.03	0.06	0.00 — −0.21	−0.01	0.04	0.00 — −0.15*	0.04	0.06	0.20 — 0.00

* Difference almost significant, ** significant, *** highly significant.

Electrocardioscanner 450 reproductions were compared with the corresponding values of 1) the conventional Mingograph 24 recordings 2) the scanner presentations of Composite Electrocardioscanner 651 3) the charter presentations of the same, and 4) the write out series of MV 1 system. The significance of differences between the series was tested with the t test. If the risk (p) was.

- $p < 0.05$ the difference was called almost significant
- $p < 0.01$ the difference was called significant and
- $p < 0.001$ the difference was called highly significant.

Results

In the comparison of the five different ECG reproductions, the corresponding durations of P wave P—R interval, and QRS interval were found to be equal.

The mean voltages, standard deviations and ranges of P R, S, and T waves and S—T deviations in the three chest leads, reproduced by the different tecniques, are presented in Table 1, where the result of the t test is also given. No significant difference in the P wave reproduction could be demonstrated between the different techniques. The values of the negative components of 9 cases of diphasic P_{V1} are lacking in the table, but the behaviour of this negative part of the deflection proved to be the same as that of the positive one.

No Q waves were found in the V1 lead, and only in two cases was a miniature Q present in the V3 lead. The only information concerning the Q wave could be obtained from the 18 patients with Q_{V5}. The mean Q_{V5} in the conventional recording was 0.10

(range 0 05—0.50) mV and the corresponding value in the Electrocardioscanner 450 presentation was 0 16 *(range* 0 00—0.35) mV Although too small for inferences, the group of Q values revealed no significant difference bet ween the five ECG presentation techni ques.

The voltages of the main ventricular depolarization deflections, R and S waves are generally lower in the tape recordings than in the conventional recordings. The ability to repeat these deflections seems to be equal in both Electrocardioscanner Model 450 and the scanner of Composite Electrocardioscanner 651 Considerable voltage defi cits are produced by both printing methods the charter of Composite Electrocardioscanner 651 and the MV 1 chain. In the case of the R wave, the difference becomes significant between the scanner display and the conventional *recording as the deflection reaches* the value 1 70 mV in the conventional *ECG (the mean voltage of R_{V3} in the* table) A significantly unequal repro*ductability is also found in the compar* ison of the repeating characteristics *of the scanner and those of the MV* 1 equipment at the level 1.39 mV in the *scanner presentation* (the mean voltage of R_{V3} in the table) The voltage losses of the R wave in the tape recording become more marked as the magnitude of the R wave increases and the most prominent voltage deficit is produced by means of the MV 1 method.

The ability to reproduce the S def lection seems to be even lower than that of the R wave in the tape recording instruments, when compared with the conventional ECG recording technique Almost significant voltage deficit is detected in the scanner display of S_{V1} and highly significant ones in those of S_{V3} and S_{V5} Still more distortion is produced by the writers although al *most significantly by the charter in* S_{V3} reproduction, and by the MV 1 system in S_{V3} and S_{V5} reproductions.

The relations of the Electrocardioscanner 450 and the Mingograph 24 presentations of the R and S waves in V1 V3 and V5 leads are given in Fig 5

According to the values shown in Table I the ability to reproduce the T wave configuration is statistically equal in all the techniques mentioned above The table includes only the initial deflections of the diphasic T waves, which appeared 5 times in V1 6 times in V3 and 7 times in V5 The results concerning the calculations performed in the terminal portions of these diphasic T waves are similar to those presented in Table I. The polarity of the T wave is always the same in corresponding ECG reproductions The shape of the *T deflection is hard to compare without* an analog to–digital converter but in a *rough inspection, the write out of the* MV 1 chain closely resembles the con *ventional ECG recording in this series.*

At the end of the QRS complex there *is often an extra* upright deflection in the scanner and charter presentation of the tape recording It will be called the post-S spike» in this investigation. This spike is a peculiarity of the scan ner and charter *reproductions, it is not* found in conventional Mingograph 24 recordings and it does not appear in the recordings written out by means of MV 1 equipment. The incidence and magnitude of the post-S spike are given in Table II In this material it is most frequent in the V3 lead, where the voltages of the R and S waves are the greatest. It is more frequent and higher in the display of the newer scanner than in that of the older model *450* Its

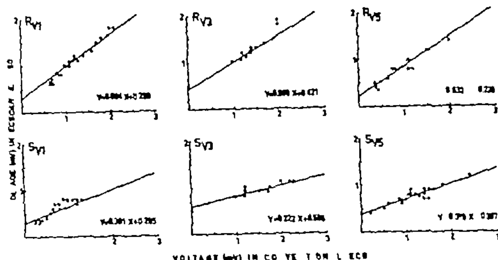


Fig 3. Regressions of R and S wave voltages in V1, V3, and V5 leads calculated from the values of Mingograf 24 recordings and corresponding Electrocardioscanner reproductions of 30 newborn infants.

incidence and magnitude are reduced in the charter procedure.

Depression of the S—T segment was present in the V1 lead in the conventional ECG of 13 infants, in the V3 lead there were 7 cases of S—T depression, and in the V5 lead the S—T deviation was positive in 6 infants and negative in one. The values of S—T deviations in different recordings are presented in Table I. Calculations have been made for the whole population. An almost significantly lower ability to reproduce S—T_{V1} deviation is established in the scanner display when compared with conventional recording. The MV 1 reproduction best resembles conventional ECG in the S—T and T regions. However the material is small and the S—T deviations are of low voltage. Thus, far reaching conclusions cannot be made according to these results. Conventional and tape recorders of this type do not repeat S—T deviations equally but at least the polarity of the deviation seems to be equal.

The U wave appeared only in V3 and V5 leads. There were 7 infants

Table II. The incidence and amplitude of the post-S spike in 30 ECG tape recordings of three chest leads reproduced by Electrocardioscanner 450 and Composite Electrocardioscanner 451.

	Electrocardioscanner 450			Composite Electrocardioscanner 451					
				scanner			charter		
Lead	No.	Mean (mV)	Range (mV)	No.	Mean (mV)	Range (mV)	No.	Mean (mV)	Range (mV)
V1	11	0.08	0.03—0.15	18	0.08	0.05—0.20	9	0.08	0.05—0.20
V3	16	0.11	0.03—0.20	27	0.13	0.05—0.30	24	0.10	0.05—0.20
V5	14	0.07	0.05—0.10	30	0.08	0.05—0.10	16	0.05	0.03—0.10

(range 0 05—0.50) mV and the corresponding value in the Electrocardioscanner 450 presentation was 0 16 (range 0 00—0.35) mV *Although too small* for inferences, the group of Q values revealed no significant difference between the five ECG presentation techniques.

The voltages of the main ventricular depolarization deflections, R and S waves are generally lower in the tape recordings than in the conventional recordings. The ability to repeat these deflections seems to be equal in both Electrocardioscanner Model 450 and the scanner of Composite Electrocardioscanner 651 Considerable voltage deficits are produced by both printing methods the charter of Composite Electrocardioscanner 651 and the MV 1 chain In the case of the R wave the *difference becomes significant* between the scanner display and the conventional recording as the deflection reaches the value 1 70 mV in the conventional ECG (the mean voltage of R_{V3} in the table) A significantly unequal reproductability is also found in the comparison of the repeating characteristics of the scanner and those of the MV 1 *equipment* at the level 1.39 mV in the scanner presentation (the mean voltage of R_{V3} in the table) The voltage losses of the R wave in the tape recording become more marked as the magnitude of the R wave increases and the most prominent voltage deficit is produced by means of the MV 1 method

The ability to reproduce the S deflection seems to be even lower than that of the R wave in the tape recording *instruments*, when compared with the conventional ECG recording technique Almost significant voltage deficit is detected in the scanner display of S_{V1} and highly significant ones in those of S_{V3} and S_{V3}. Still more distortion is produced by the *writers*, although almost significantly by the charter in S_{V3} reproduction, and by the MV 1 system in S_{V3} and S_{V5} reproductions.

The relations of the Electrocardioscanner 450 and the Mingograph 24 presentations of the R and S waves in V1 V3 and V5 leads are given in Fig 5

According to the values shown in Table I the *ability to reproduce* the T wave configuration is statistically equal in all the techniques mentioned above. The table includes only the initial deflections of the diphasic T waves, which appeared 5 times in V1 6 times in V3, and 7 times in V5 The results concerning the calculations performed in the terminal portions of these diphasic T waves are similar to those presented in Table I. The polarity of the T wave *is always* the same in corresponding ECG reproductions. The shape of the T deflection is hard to compare without an analog to-digital converter but in a rough inspection, the write out of the MV 1 chain closely resembles the conventional ECG recording in this series.

At the end of the QRS complex there is often an extra upright deflection in the scanner and charter presentation of the tape recording It will be called the *post-S spike in this investigation*. This spike is a peculiarity of the scanner and charter reproductions, *it is not* found in conventional Mingograph 24 recordings and it does not appear in the recordings written out by means of MV 1 equipment. The incidence and magnitude of the post-S spike are given in Table II In this material it is most frequent in the V3 lead, where the voltages of the R and S waves are the greatest. It is more frequent and higher in the display of the newer scanner than *in that of the older model* 450 Its

voltages of the R wave, and particularly the S wave, is found in reproductions of tape recordings when compared with corresponding conventional electrocar diograms. An explanation for these voltage distortions is obviously the restricted frequency response (0 5—100 cps) of the Electrocardiocorder The recommendations of the American Heart Association [9] call for a frequency response of 0 05 — over 500 cps for direct writing electrocardiographs, and that of frequency modulated tape recorders must reach the value of more than 100 cps. According to the recorder scanner and recorder-charter system frequency response curves of Hinkle et al., the effective frequency range is 0.5—50 cps [35] Thus a noticeable amount of the electrocardiographic frequency spectrum falls outside the response of this tape recording equipment.

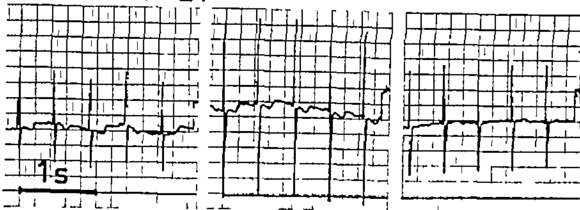
The effect of poor high-frequency response on ECG has been reported to be an increasing attenuation of R and S voltages with decreasing frequency response. The effect on the amplitude of the S deflection is more marked [53] In ECG writers the mass of the stylus and its friction against the paper fur ther limit the high frequency response below the limits of the circuitry The results of the present investigation are in agreement with these facts and also with the report f Hinkle et al. [35]

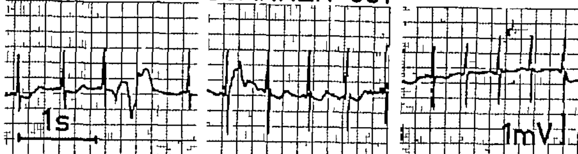
The restriction of low frequency response of the electrocardiograph leads to inaccuracy in repeating wave forms containing lower frequency components, i e. P S—T and T (U) deflections, cor rectly Thus a progressive attenuation of T wave voltage, and also an increase of S wave amplitude, have been report ed to be produced by deteriorating low frequency response [53] Only a minimal and not significant deficit of T wave amplitude was observed in the tape recording presentations of the present study A minimal S—T segment depression and post T sag have been also considered as artifacts caused by degenerated low frequency cut-off [35 53] These findings have already been described in Electrocardiocorder-scanner presentations [27] Significant dif ferences were found in the present in vestigation between the corresponding recordings in their ability to reproduce S—T deviation, but the S—T depressions did not prove to increase in tape recording reproductions. Because of the inaccuracy of the information available concerning the reproductibility of the S—T segment in the instruments of Holter Avionics, and because of the importance of this segment in the diag nosis of coronary heart diseases, this area calls for more investigation.

Attention has not been paid earlier to the post-S spike, a common finding in the present study This spike is a small overshoot after a prominent S wave, and deep S waves are not so common in left precordial leads among adults investigated earlier by means of this technique.

CONCLUSIONS

The Electrocardiocorder AVSEP tape recording system of Holter Avionics is a valuable tool when long-term ECG recordings are to be studied. By means of the modified electrode design, and in standardized test conditions, an interference-free recording of unipolar chest leads (V1 V2, and V5) can be obtained. Suddenly appearing altera-





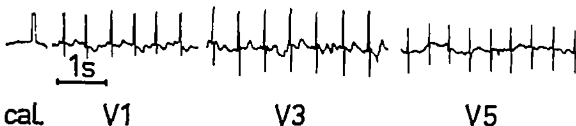


Fig. 6 Comparison of Mingograf 24 recording and corresponding tape recording reproduced by Composite Electrocardioscanner 651 and Electrocardioscanner 450 — MV 1 technique.

with U_{V3} in some of the 5 reproductions, but only 2 cases with U_{V3} in all corresponding reproductions U_{V5} was detected in 2 infants, and it was not repeated correspondingly at all. The maximal amplitude of this deflection was 0 10 mV The comparison of Mingograph 24 recording and corresponding tape recording reproduced by Composite Electrocardioscanner 651 and Electrocardioscanner 450—MV 1 technique is presented in Fig 6

Comments

The values obtained by conventional technique, which are presented in Table I are of the same magnitude as those reported by Ziegler [112] Wasserburger [110] and Walsh [104 107] The means and maximum values of the *R* and *S* waves seem to be a little lower in this material as they were in the earlier study of our group [98]

A *considerable attenuation* of the

voltages of the R wave, and particularly the S wave, is found in reproductions of tape recordings when compared with corresponding conventional electrocardiograms. An explanation for these voltage distortions is obviously the restricted frequency response (0.5—100 cps) of the Electrocardiocorder. The recommendations of the American Heart Association [9] call for a frequency response of 0.05 — over 500 cps for direct writing electrocardiographs, and that of frequency modulated tape recorders must reach the value of more than 100 cps. According to the recorder scanner and recorder-charter system frequency response curves of Hinkle et al., the effective frequency range is 0.5—50 cps [25]. Thus a noticeable amount of the electrocardiographic frequency spectrum falls outside the response of this tape recording equipment.

The effect of poor high-frequency response on ECG has been reported to be an increasing attenuation of R and S voltages with decreasing frequency response. The effect on the amplitude of the S deflection is more marked [53]. In ECG writers the mass of the stylus and its friction against the paper further limit the high-frequency response below the limits of the circuitry. The results of the present investigation are in agreement with these facts and also with the report of Hinkle et al. [25].

The restriction of low frequency response of the electrocardiograph leads to inaccuracy in repeating wave forms containing lower frequency components, i.e. P, S—T and T *(U) deflections*, correctly. Thus a progressive attenuation of T wave voltage, and also an increase of S wave amplitude, have been reported to be produced by deteriorating low frequency response [53]. Only a minimal and not significant deficit of T wave amplitude was observed in the tape recording presentations of the present study. A minimal S—T segment depression and post T sag have been also considered as artifacts caused by degenerated low frequency cut-off [35, 53]. These findings have already been described in Electrocardiocorder-scanner presentations [27]. Significant differences were found in the present investigation between the corresponding recordings in their ability to reproduce S—T deviation, but the S—T depressions did not prove to increase in tape recording reproductions. Because of the inaccuracy of the information available concerning the reproductibility of the S—T segment in the instruments of Holter Avionics, and because of the importance of this segment in the diagnosis of coronary heart diseases, this area calls for more investigation.

Attention has not been paid earlier to the post-S spike, a common finding in the present study. This spike is a small overshoot after a prominent S wave, and deep S waves are not so common in left precordial leads among adults investigated earlier by means of this technique.

CONCLUSIONS

The Electrocardiocorder-AVSEP tape recording system of Holter-Avionics is a valuable tool when long-term ECG recordings are to be studied. By means of the modified electrode design, and in standardized test conditions, an interference-free recording of unipolar chest leads (V1, V3, and V5) can be obtained. Suddenly appearing altera

tions of an ECG pattern are rather easily detected in the play back by means of the Electrocardioscanner and these segments of the tape recording can be transformed into regular paper reproductions with the Electrocardiocharter or the MV 1 equipment described here

The time axis of the devices has been proved to be accurate enough for electrocardiographic research when the timing errors have been eliminated by careful calibration, repeated marking (e.g changing of leads) and conscientious diary keeping

The electronic properties of the equipment cause some distortions of the voltage axis on the reproductions of the tape recording when compared to a corresponding conventional ECG recording Because of the limited frequency response of the tape recording instruments the voltage of the deflections with high frequency components, especially that of the S wave, is reproduced significantly attenuated. The same reason is responsible for distortion of the deflections with low frequency components. Thus almost significant differences appear between conventional and tape recording instruments in their ability to repeat S—T deviations. This will be very important in the diagnosis of coronary heart diseases.

The distortions found in the Electrocardioscanner display are often increased in both writing out methods. The unpracticalness of the use of the former Electrocardiocharter Model 550 has been eliminated in the construction of the modern Composite Electrocardioscanner 651

SECTION II LONG TERM ECG TAPE RECORDINGS OF NEWBORN INFANTS

MATERIAL AND METHODS

Material

The material consisted of 90 newborn infants, 50 of whom were born at term. The full term infants were examined at the Municipal Maternity Hospital of Turku, and the premature series in the neonatal wards of the Children's Hospital of the University of Turku in 1964—1968. The birth weight distribution of the material is presented in Table III.

In the full-term group there were 22 boys and 28 girls. They were infants of primiparas in 30 cases and of multiparas in 20 cases. 16 of the mothers had received antihypertensive treatment, mainly chlortiazid derivatives, during pregnancy. Of these, 14 had a blood pressure of more than 140/90 before delivery; only 2 showed other signs, albeit mild ones, of toxaemia. Abnormalities in the foetal heart sounds during delivery were detected in 2 cases. The delivery was normal except in 3 cases: one infant was born in deflexion attitude, one in breech presentation, and one by means of vacuum extraction because of signs of foetal asphyxia. The cord was clamped routinely late, i.e. after cessation of umbilical artery pulsations, but in 10 cases the cord was clamped early, immediately after the child was born. 47 of the infants had an Apgar score of 8—10, 2 babies had 7 points, and the baby delivered by vacuum extraction had only 5 points. All the infants recovered without any special resuscitative procedures. In a careful physical examination they showed no signs of cardiopulmonary or neurological disorders during the recording procedure or during their later stay at the hospital.

The series of premature infants included 19 boys and 21 girls. 22 of them were children of primiparas, and 6 infants were twins (5 A babies, and one B baby). 9 of the mothers had received antihypertensive drugs during

Table III. Birth weight distribution of the material of 50 full-term and 40 premature newborn infants with birth weights of [illegible]—[illegible] g.

Birth weight	Number of infants
Premature infants	
under 1000 g	1
1000—1500	8
1500—2000	14
2000—2500	15
Full-term infants	
2500—3000 g	4
3000—3500	20
3500—4000	13
4000—4500	11
over 4500	2
Total	90

tions of an ECG pattern are rather easily detected in the play back by means of the Electrocardioscanner and these segments of the tape recording can be transformed into regular »paper reproductions» with the Electrocardiocharter or the MV 1 equipment described here

The time axis of the devices has been proved to be accurate enough for electrocardiographic research when the timing errors have been eliminated by careful calibration repeated marking (e.g changing of leads) and conscientious diary keeping

The electronic properties of the equipment cause some distortions of the voltage axis on the reproductions of the tape recording when compared to a corresponding conventional ECG recording Because of the limited frequency response of the tape recording instruments, the voltage of the deflections with high frequency components, especially that of the S wave, is reproduced significantly attenuated. The same reason is responsible for distortion of the deflections with low frequency components. Thus, almost significant differences appear between conventional and tape recording instruments in their ability to repeat S—T deviations. This will be very important in the diagnosis of coronary heart diseases.

The distortions found in the Electrocardioscanner display are often increased in both writing out methods. The unpracticalness of the use of the former Electrocardiocharter Model 550 has been eliminated in the construction of the modern Composite Electrocardioscanner 651

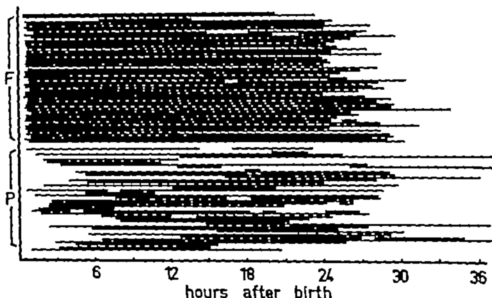


Fig. 7 The periods of ECG tape recording in 50 full-term (F) and 40 premature (P) new born infants.

potassium and calcium content were taken from the cord veins, centrifuged immediately and sent to the laboratory for flame photometric (potassium) and titrimetric (calcium) determination. In the full-term group 41 succesfull determinations of serum potassium and 26 of serum calcium concentration were made. Serum calcium was determined in 4 premature infants using the same methods and the same kind of blood samples, but the potassium content was analysed from microsamples containing capillary blood, in 25 premature infants. All the concentrations represent the electrolyte status at the beginning of the tape recording.

For clinical reasons only the actual acid-base balance was defined according to the micro-Astrup method. Therefore, these determinations were made especially in children who had asphyctic disorders. They were performed only in 18 premature infants.

The analysis of the tape recordings was performed by means of Electro-cardioscanner Model 450 and the MV 1 method described in section I (page 20).

The initial ECG pattern was photographed on the AVSEP screen in each lead. Otherwise, the different quantities were measured on the screen directly. Thus, every tape was carefully examined, measuring the rather stable voltages of the P, Q, R, S, T and U waves, S-T deviations, and the durations of P wave, P-R, QRS, Q-T and R-R intervals. The heart rate was calculated from the R-R interval on the AVSEP screen, the Arrhythmiagraph was employed for this purpose only in the frequencies below 85/min. The basal ECG configuration, basal heart rate, minimum and maximum heart rates fo each hour were estimated. Thus, slowly developing changes of the ECG pattern could be demonstrated. The time corrections were made according to the real time clock and the diary.

The durations of bradycardias below 90/min and tachycardias over 170/min

pregnancy but 14 of them had a blood pressure higher than 140/90 mm Hg measured before or during delivery in the obstetric department. There were 3 mild toxaemias among the mothers, one mother had an actual eclampsia, and one had a grave uraemia. Abnormal foetal heart sounds were found in 2 deliveries. There were 10 exceptional deliveries in this material one infant was born in deflection attitude 4 were pelvic breech deliveries and 5 infants were born by caesarean section. One additional infant was born at home, but she was in quite good condition on arrival at the hospital. No early clamping of the umbilical cord was performed in this series. The Apgar scores one minute after birth were 8—10 in 19 infants 4—7 in 15 infants and 0—3 in 6 infants. Although quite nonhomogenous in its obstetric history the group of premature infants could be paediatrically divided into two quite uniform groups 30 infants who showed no signs of neonatal cardiopulmonary or neurological disorders and 10 infants with a clinical picture of moderate to grave asphyxia lasting throughout the ECG examination 3 of whom died during the electrocardiographic registration. The infants were brought to the neonatal ward mainly because of prematurity at ages ranging from a few minutes to a couple of hours. Therefore the electrocardiographic examination could not be started systematically at birth. On the other hand, these babies stayed a longer time in hospital and they could be clinically examined more throughly than the full term group No infant in either full term or premature group had received digitalis or other cardioactive drugs.

Clinical and laboratory methods

In the full term infant group the electrocardiographic tape recording was started as soon as possible after the newborn baby had been removed from delivery room to nursery washed, and placed in bed. The preparation of the skin, the electrode attachment, and the recording technique have been described in section I (page 18) Electrocardiocorder Model 350 A was utilized for recording and three chest leads, V1 V3 and V5 were followed successively At the beginning of the recording an initial registration, using each lead for 10 minutes, was carried out thereafter the lead was changed every one hour Each recording was started by the author himself, and later the leads were selected according to a routine scheme by the nurses. A diary was kept of these functions and also of all nursing procedures and phenomena observed in the subject (crying, feeding, etc.)

The same registration method was employed when examining the infants belonging to the premature group but the recording was often started later than in the full term group, because many of the premature infants were sent to our neonatal wards from other hospitals. Also there were more often factors (e.g nursing and resuscitation procedures, respirator treatment) disturbing the ECG recording The recording times of the full term and premature series are presented in Fig 7

To control the effects of the main non-circulatory factors affecting the ECG the serum potassium and calcium concentration, rectal temperature and, in the premature group, acid base balance, were determined. In the full term infants, the blood samples for

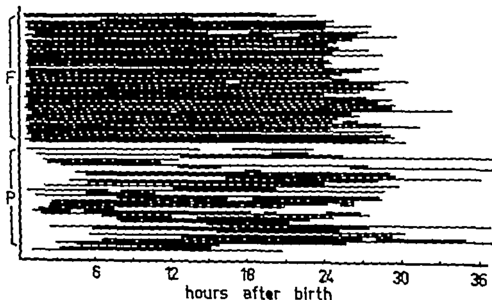


Fig. 7 The periods of ECG tape recording in 50 full-term (F) and 40 premature (P) new born infants.

potassium and calcium content were taken from the cord veins, centrifuged immediately and sent to the laboratory for flame photometric (potassium) and titrimetric (calcium) determination. In the full-term group 41 successfull determinations of serum potassium and 26 of serum calcium concentration were made. Serum calcium was determined in 4 premature infants using the same methods and the same kind of blood samples, but the potassium content was analysed from microsamples containing capillary blood, in 25 premature infants. All the concentrations represent the electrolyte status at the beginning of the tape ecording.

For clinical reasons only the actual acid-base balance was defined according to the micro-Astrup method. Therefore, these determinations were made especially in children who had asphyctic disorders. They were performed only in 18 premature infants.

The analysis of the tape recordings was performed by means of Electrocardioscanner Model 450 and the MV 1 method described in section I (page 20).

The initial ECG pattern was photographed on the AVSEP screen in each lead. Otherwise, the different quantities were measured on the screen directly. Thus, every tape was carefully examined, measuring the rather stable voltages of the P, Q, R, S, T and U waves, S-T deviations, and the durations of P wave, P-R, QRS, Q-T and R-R intervals. The heart rate was calculated from the R-R interval on the AVSEP screen, the Arrhythemia graph was employed for this purpose only in the frequencies below 85/min. The basal ECG configuration, basal heart rate, minimum and maximum heart rates for each hour were estimated. Thus, slowly developing changes of the ECG pattern could be demonstrated. The time corrections were made according to the real time clock and the diary.

The durations of bradycardias below 90/min and tachycardias over 1 0/min

pregnancy but 14 of them had a blood pressure higher than 140/90 mm Hg measured before or during delivery in the obstetric department. There were 3 mild toxaemias among the mothers, one mother had an actual eclampsia and one had a grave uraemia. Abnormal foetal heart sounds were found in 2 deliveries. There were 10 exceptional deliveries in this material one infant was born in deflection attitude 4 were pelvic breech deliveries and 5 infants were born by caesarean section One additional infant was born at home but she was in quite good condition on arrival at the hospital. No early clamping of the umbilical cord was performed in this series. The Apgar scores one minute after birth were 8—10 in 19 infants 4—7 in 15 infants and 0—3 in 6 infants. Although quite nonhomogenous in its obstetric history the group of premature infants could be paediatrically divided into two quite uniform groups 30 infants who showed no signs of neonatal cardiopulmonary or neurological disorders and 10 infants with a clinical picture of moderate to grave asphyxia lasting throughout the ECG examination, 3 of whom died during the electrocardiographic registration. The infants were brought to the neonatal ward mainly because of prematurity at ages ranging from a few minutes to a couple of hours Therefore, the electrocardiographic examination could not be started systematically at birth. On the other hand, these babies stayed a longer time in hospital and they could be clinically examined more throughly than the full term group No infant in either full term or premature group had received digitalis or other cardioactive drugs.

Clinical and laboratory methods

In the full term infant group the electrocardiographic tape recording was started as soon as possible after the newborn baby had been removed from delivery room to nursery washed, and placed in bed. The preparation of the skin, the electrode attachment, and the recording technique have been described in section I (page 18) Electrocardiocorder Model 350 A was utilized for recording, and three chest leads, V1 V3 and V5 were followed successively At the beginning of the recording, an initial registration, using each lead for 10 minutes, was carried out thereafter the lead was changed every one hour Each recording was started by the author himself and later the leads were selected according to a routine scheme by the nurses. A diary was kept of these functions and also of all nursing procedures and phenomena observed in the subject (crying, feeding, etc.)

The same registration method was employed when examining the infants belonging to the premature group but *the recording was often started* later than in the full term group, because many of the premature infants were sent to our neonatal wards from other hospitals. Also there were more often factors (e.g nursing and resuscitation procedures, respirator treatment) disturbing the ECG recording The recording times of the full term and premature series are presented in Fig 7

To control the effects of the main non-circulatory factors affecting the ECG the serum potassium and calcium concentration, rectal temperature and, in the premature group, acid base balance, were determined. In the full term infants, the blood samples for

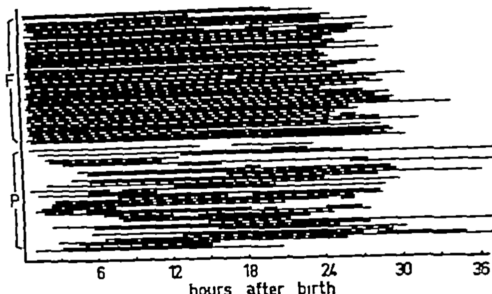


Fig. 7 The periods of ECG tape recording in 80 full-term (F) and 40 premature (P) new born infants.

potassium and calcium content were taken from the cord veins, centrifuged immediately and sent to the laboratory for flame photometric (potassium) and titrimetric (calcium) determination. In the full term group, 41 succesfull determinations of serum potassium and 26 of serum calcium concentration were made. Serum calcium was determined in 4 premature infants using the same methods and the same kind of blood samples, but the potassium content was analysed from microsamples containing capillary blood, in 23 premature infants. All the concentrations represent the electrolyte status at the beginning of the tape recording.

For clinical reasons only the actual acid-base balance was defined according to the micro-Astrup method. Therefore, these determinations were made especially in children who had asphyctic disorders. They were performed only in 18 premature infants.

The analysis of the tape recordings was performed by means of Electrocardioscanner Model 4.0 and the M[illegible] method described in section I (page [illegible]

The initial ECG pattern was photographed on the AVSEP screen in each lead. Otherwise, the different quantities were measured on the screen directly. Thus, every tape was carefully examined, measuring the [illegible] stable voltages of the P, Q, R, S, T and U waves, S-T deviations and the durations of P wave, P-R, QRS, Q-T and R-R intervals. The heart rate was calculated from the R-R interval on the AVSEP screen; the [illegible]graph was employed for this purpose only in the frequencies below [illegible]. The basal ECG configuration [illegible] heart rate minimum and [illegible] heart rates for each [illegible] mated. Thus, [illegible] of the ECG pattern [illegible] strated. The [illegible] made according [illegible] and the diag[illegible]

The duration of [illegible] 56 min [illegible]

were evaluated Also irregularities in cardiac rhythm and activation were timed, compared with observations of the diary and when necessary ana lysed *in detail by photographing* or by writing out the signal on ECG paper in the manner presented in section I (page 20)

Statistical methods

The data thus listed were punched on cards, and the heart rate patterns, ECG voltage patterns, and changes of various intervals were calculated and plotted in relation to the parameters available by an IBM 1130 computer Rarely appearing phenomena like sud den electrocardiographic alterations were studied directly without data processing

The differences between the series were tested by means of the t test. The statistical significance was esti *mated as mentioned in section I* (page 25)

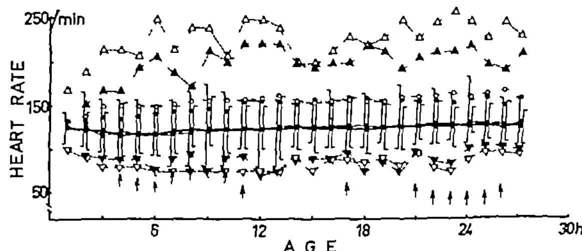


Fig. 8. Heart rate patterns of 50 full term and 30 healthy premature infants. O——O mean basal heart rate of full term, ●——● mean basal heart rate *of premature*] *range* of mean basal heart rate of full term, [range of mean basal heart rate of premature O O mean maximal heart rate of full term, ● ● mean maximal heart rate of premature △ △ peak heart rate values of full term ▲ ▲ peak heart rate values of premature, ▽ ▽ minimum heart rate values of full term, ▼ ▼ *minimum heart* rate values of premature. Minimum values of 10 asphyctic premature infants differing from those of the healthy premature group are marked with arrows.

HEART RATE PATTERNS

Results

Mean heart rates

The mean basal heart rates, their ranges, and the minimal and maximal, as well as the mean maximum rates for both full-term and healthy premature infants during the observation period are presented in Fig. 8. The curves of premature babies start in the 2nd hour and all the curves have been cut at the 27th hour because of the insufficient number of observations outside this segment. The curves are only for healthy children, although analysis revealed no significant differences between mean heart rate levels of healthy and asphyctic infants.

There are no significant differences between the mean basal heart rates of full-term and premature infants in the whole material. The basal rates reach their minima at the age of 3—6 hours. Thereafter the values gradually increase, exceeding the first hour values of 125/min at the age of 12 hours until the level of 130/min is achieved at the end of the first day of life. The ranges are practically equal although the maximal basal heart rates of premature infants tend to be lower than those of the full-term. There were no significant differences between the basal heart rates of boys and girls, between those of children of primiparas and multiparas in the whole material or between the basal rates of full-term cases with early and late clamped umbilical cord. Neither were any significant differences found between the basal heart rates of the 3 Apgar score groups nor between those of the children of hypertensive and non-hypertensive mothers. Fig 8 shows that the mean basal heart rate is almost equal in the full term and healthy premature infants. The form of the mean heart rate curve of the prematures remains almost equal when the 10 asphyctic cases are included.

The effect of birth weight on the mean basal heart rate was studied by dividing the healthy material into four groups: I birth weight < 2000 g; II 2000—2500 g; III 2500—3500 g; and IV birth weight > 3500 g. The mean heart rate curves of these groups are shown in Fig 9. There are significant differences between the basal heart rates of small and larger premature babies (groups I and II) from the beginning to the 19th hour of life, and between those of groups III and IV of full term infants up to the age of 24 hours. The period of low basal cardiac rate is most marked in groups II and III. The groups of small premature and large full-term infants have higher basal heart rate values, and the level of basal cardiac frequency remains more constant during the first 24 hours, especially in group I.

There was a low positive correlation (correlation coefficients of 0.37 and 0.22 for full-term and premature infants) between the first basal heart rate value and the corresponding rectal temperature in the whole material. The basal heart rate did not correlate with the serum calcium or potassium content of the material. The values of these parameters are given in Table IV.

When the lower edge of the basal heart rate was considered, it was found that there was a tachycardic group of 14 per cent of the whole material, in which the basal rate was never below 125/min during the observation period.

were evaluated. Also irregularities in cardiac rhythm and activation were timed, compared with observations of the diary and, when necessary analysed in detail by photographing or by writing out the signal on ECG paper in the manner presented in section I (page 20)

Statistical methods

The data thus listed were punched on cards, and the heart rate patterns, ECG voltage patterns, and changes of *various intervals* were calculated and plotted in relation to the parameters available by an IBM 1130 computer Rarely appearing phenomena like sudden electrocardiographic alterations were studied directly without data processing

The differences between the series were tested by means of the t test. The statistical significance was estimated as mentioned in section I (page 25)

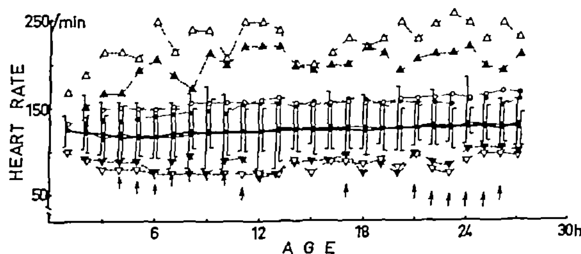


Fig. 8. Heart rate patterns of 50 full term and 30 healthy premature infants. O——O *mean* basal heart rate of full term, ●——● mean basal heart rate of premature,] range of mean basal heart rate of full term, [range of mean basal heart rate of premature O O mean maximal heart rate of full term, ● ● mean maximal heart rate of premature △ △ peak heart rate values of full term, ▲ ▲ peak heart rate values of premature, ▽ ▽ *minimum heart rate values of full term*, ▼ ▼ minimum heart rate values of premature. Minimum values of 10 asphyctic premature infants differing from those of the healthy premature group are marked with arrows.

HEART RATE PATTERNS

Results

Mean heart rates

The mean basal heart rates, their ranges, and the minimal and maximal, as well as the mean maximum rates for both full term and healthy premature infants during the observation period are presented in Fig 8 The curves of premature babies start in the 2nd hour and all the curves have been cut at the 27th hour because of the insufficient number of observations outside this segment. The curves are only for healthy children, although analysis revealed no significant differences between mean heart rate levels of healthy and asphyctic infants.

There are no significant differences between the mean basal heart rates of full term and premature infants in the whole material. The basal rates reach their minima at the age of 3—6 hours. Thereafter the values gradually increase, exceeding the first-hour values 1 125/min at the age of 12 hours until the level of 130/min is achieved at the end of the first day of life. The ranges are practically equal although the maximal basal heart rates of premature infants tend to be lower than those of the full-term. There were no significant differences between the basal heart rates of boys and girls between those of children of primiparas and multiparas in the whole material, or between the basal rates of full-term cases with early and late clamped umbilical cord. Neither were any significant differences found between the basal heart rates of the 3 Apgar score groups nor between those of the children of hypertensive and non-hypertensive mothers. Fig 8 shows that the mean basal heart rate is almost equal in the full-term and healthy premature infants. The form of the mean heart rate curve of the prematures remains almost equal when the 10 asphyctic cases are included.

The effect of birth weight on the mean basal heart rate was studied by dividing the healthy material into four groups I birth weight < 2000 g II 2000—2500 g III 2500—3500 g and IV birth weight > 3500 g. The mean heart rate curves of these groups are shown in Fig. 9 There are significant differences between the basal heart rates of small and larger premature babies (groups I and II) from the beginning to the 19th hour of life, and between those of groups III and IV of full-term infants up to the age of 24 hours. The period of low basal cardiac rate is most marked in groups II and III. The groups of small premature and large full term infants have higher basal heart rate values, and the level of basal cardiac frequency remains more constant during the first 24 hours, especially in group I.

There was a low positive correlation (correlation coefficients of 0.37 and 0.22 for full term and premature infants) between the first basal heart rate value and the corresponding rectal temperature in the whole material. The basal heart rate did not correlate with the serum calcium or potassium content of the material. The values of these parameters are given in Table IV

When the lower edge of the basal heart rate was considered, it was found that there was a tachycardic group of 14 per cent of the whole material, in which the basal rate was never below 125/min during the observation period.

were evaluated. Also irregularities in cardiac rhythm and activation were timed, compared with observations of the diary and, when necessary analysed in detail by photographing or by writing out the signal on ECG paper in the manner presented in section I (page 20)

Statistical methods

The data thus listed were punched on cards, and the heart rate patterns ECG voltage patterns, and changes of various intervals were calculated and plotted in relation to the parameters available, by an IBM 1130 computer Rarely appearing phenomena like sudden electrocardiographic alterations were studied directly without data processing

The differences between the series were tested by means of the t test. The statistical significance was estimated as mentioned in section I (page 25)

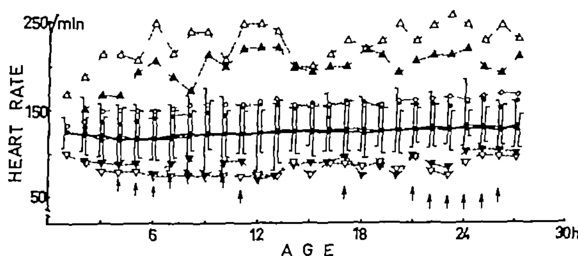


Fig. 8. Heart rate patterns of 50 full term and 30 healthy premature infants. O——O mean basal heart rate of full term, ●——● mean basal heart rate of premature,] range of mean basal heart rate of full term, [range of mean basal heart rate of premature, O O mean maximal heart rate of full term, ● ● mean maximal heart rate of premature △ △ peak heart rate values of full term, ▲ ▲ peak heart rate values of premature, ▽ ▽ minimum heart rate values of full term, ▼ ▼ minimum heart rate values of premature Minimum values of 10 asphyctic premature infants differing from those of the healthy premature group are marked with arrows.

HEART RATE PATTERNS

Results

Mean heart rates

The mean basal heart rates, their ranges, and the minimal and maximal, as well as the mean maximum rates for both full term and healthy premature infants during the observation period are presented in Fig 8. The curves of premature babies start in the 2nd hour and all the curves have been cut at the 27th hour because of the insufficient number of observations outside this segment. The curves are only for healthy children, although analysis revealed no significant differences between mean heart rate levels of healthy and asphyctic infants.

There are no significant differences between the mean basal heart rates of full-term and premature infants in the whole material. The basal rates reach their minima at the age of 3—8 hours. Thereafter the values gradually increase, exceeding the first-hour values of 123/min at the age of 12 hours until the level of 130/min is achieved at the end of the first day of life. The ranges are practically equal although the maximal basal heart rates of premature infants tend to be lower than those of the full-term. There were no significant differences between the basal heart rates of boys and girls between those of children of primiparas and multiparas in the whole material or between the basal rates of full-term cases with early and late clamped umbilical cord. Neither were any significant differences found between the basal heart rates of the 3 Apgar score groups nor between those of the children of hypertensive and non-hypertensive mothers. Fig 8 shows that the mean basal heart rate is almost equal in the full term and healthy premature infants. The form of the mean heart rate curve of the prematures remains almost equal when the 10 asphyctic cases are included.

The effect of birth weight on the mean basal heart rate was studied by dividing the healthy material into four groups: I birth weight < 2000 g II 2000—2500 g III 2500—3500 g and IV birth weight > 3500 g. The mean heart rate curves of these groups are shown in Fig 9. There are significant differences between the basal heart rates of small and larger premature babies (groups I and II) from the beginning to the 19th hour of life, and between those of groups III and IV of full-term infants up to the age of 24 hours. The period of low basal cardiac rate is most marked in groups II and III. The groups of small premature and large full-term infants have higher basal heart rate values, and the level of basal cardiac frequency remains more constant during the first 24 hours, especially in group I.

There was a low positive correlation (correlation coefficients of 0.37 and 0.22 for full-term and premature infants) between the first basal heart rate value and the corresponding rectal temperature in the whole material. The basal heart rate did not correlate with the serum calcium or potassium content of the material. The values of these parameters are given in Table IV.

When the lower edge of the basal heart rate was considered, it was found that there was a tachycardic group of 14 per cent of the whole material, in which the basal rate was never below 125/min during the observation period.

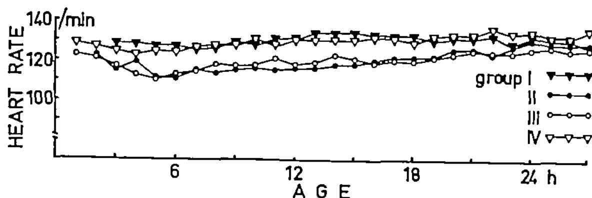


Fig. 9 Mean basal heart rates of infants with birth weight of (I) < 2000 g, (II) 2000—2500 g (III) 2500—3500 g, and (IV) > 3500 g.

In most infants, 70 per cent, the lower limit of the basal cardiac frequency was 100/min, but in the remaining 16 per cent of the material there were periods lasting several hours with a basal rate lower than 100/min. The distribution of the cases with basal heart rates below 125/min was equal in the full term, healthy and asphyctic premature materials. The tachycardic heart rate was present in 6 full term and 7 premature infants The difference between the incidences of this pattern in the full term and premature groups is highly significant. All the cases with tachycardic basal frequency belonged to the birth weight groups I and IV except one infant weighing 3340 g

Minimal and maximal heart rates

The lower edge of the cardiac frequency range was just the same in full term and healthy premature babies, as can be seen in Fig 8 When the means of minimum heart rate values of the healthy in the whole material for each hour were calculated, the curves thus obtained closely resembled the minimum curves of the healthy cases in Fig 8 The lowest mean minimum heart rates appeared at the age of 4—6 hours, which corresponds well to the period of lowest mean basal heart rate. No differences could be demonstrated between the minimum heart rates of the healthy premature and full term infants. The lowest heart rate of both healthy premature and full term groups was 85/min. The bradycardic tendency of the asphyctic newborn is shown in Fig 8 by marking the deviations of the lower edge of the frequency range of the asphyctic premature from that of the normal premature with arrows. These asphyctic bradycardias reached the limit of 50/min, with the rhythm disturbances of dying heart excluded.

Special attention was paid to the occurrence of bradycardias below the value of 90/min. The incidence of cases with heart rate below this value is presented in Table V The accumulation of these bradycardias in females is statistically almost significant. It can be seen that bradycardias appear in almost every asphyctic premature The total number of sudden bradycardias was 48 during the recording time of 1248 hours in full term 22 during 614 hours in healthy premature and 38 during

T bl IV Rectal temperature, serum potassium, and calcium values at the beginning of recording in 60 full-term and 40 premature infants.

Material	Rectal temperature (°C)			Serum potassium (mEq/1)			Serum calcium (mg/100 ml)		
	No. of cases	mean	range	No. of cases	mean	range	No. of cases	mean	range
Full-term	50	35.5	33.4 — 37.0	41	5.2	4.0 — 7.4	28	11.1	9.2 — 13.1
Premature	40	35.1	33.2 — 36.9	25	4.4	4.3 — 8.8	4	10.3	9.5 — 10.9

120 hours in asphyctic premature infants. The frequency of the brady cardic phases is nearly the same among the healthy infants, but 10 times higher among the asphyctic infants. The du ration of the bradycardias was less than 1/ min in 2/3 of the total number of bradycardias in the full term in 1/3 of that in the healthy prematures and in 1/4 of that in the asphyctic premature material. Thus the premature infants, especially asphyctic ones, had a tendency to longer bradycardias. Maximal reversible bradycardia in asphyctic children lasted 35 min. No correlation of bradycardias with exter nal observations of the subject was established, although in asphyctic babies they often occurred during apnoeic at tacks. Nor was any relation detected with the age of the baby

The upper limit of the cardiac frequency range seems to be higher in full-term than in premature infants in Fig. 8 The inclusion of asphyctic cases does not alter the maximum values of the healthy premature. In Fig. 8 there are also the mean maximum heart rate curves, which differ significantly dur ing the first 10 hours. The maximal frequency for full-term babies was 260/ min, that of premature ones was 222/ min.

The duration and number of tachy cardias with a rate over 170/min were estimated. The distribution of cases with one or more tachycardias of this kind between the sexes, and between the full-term and premature groups, is presented in Table V No differences could be demonstrated between the healthy groups and between the sexes, but between the asphyctic and healthy prematures a highly significant dif

Table V Number of infants with bradycardias of less than 90/min and tachycardias of more than 170/min in ECG tape recordings of 90 newborn infants.

Material	Bradycardias <90	Tachycardias >170
50 full term infants	15 (30.0 %)	40 (80.0 %)
22 boys	4 (18.2 %)	17 (77.2 %)
28 girls	11 (39.2 %)	23 (82.1 %)
30 *healthy premature*	9 (30.0 %)	24 (80.0 %)
13 boys	2 (15.4 %)	10 (76.9 %)
17 girls	7 (41.2 %)	14 (82.4 %)
10 asphyctic premature	9 (90.0 %)	5 (50.0 %)
6 boys	6 (100.0 %)	3 (50.0 %)
4 girls	3 (75.0 %)	2 (50.0 %)

ference was observed The total number of these tachycardias, grouped also according to their duration and their relative incidences (1/recording hour) are given in Table VI The total relative incidences are practically the same in the healthy groups, but a clearly lower value is obtained in the asphyctic group The duration is usually under 15 min. The maximal duration of this kind of sinus tachycardia was 60 min in full term infants, and 20 min in premature infants. Table VI also shows the incidences of tachycardias accompanied by T wave changes, usually lowering or inversion, and shortening of P R interval. These changes were most frequent in healthy prematures, but they were not identified in asphyctic cases at all. The most common report in the diary during the tachycardias was spontaneous crying, but they were also associated with injections, taking of blood samples physical examination, controlling of temperature heart and respiratory rates, suction of mucus, and the finding of wet swaddling clothes !

Heart rate variation

All the 50 full term infants had a minimal continuous irregularity of heart rate which will be called here phasic variation. This term was characterized and introduced for long term recordings of the heart rate of newborn infants by Urbach et al. [93] It corresponds to minimal, »normal sinus arrhythmia but the former term is preferable because in continuous recording, the heart rate is really varying all the time, but the phenomenon is not a real arrhythmia The criteria of phasic variation can be applied directly to Arrhythmiagraphic» presentation [93] In the AVSEP display this pattern is seen as a continuous horizontal movement of the terminal tail of the ECG complex it is also heard as a fluctuation of the tune of the loudspeaker In the AVSEP phasic variation was detected also in very high heart rates of the magnitude of 260/min, where the Arrhythmiagraph failed to demonstrate the phenomenon.

Table VI. Incidence of tachycardias with heart rate of more than 170/min and association of T wave and P R interval changes with them in ECG tape recordings of 99 newborn infants.

Material	Number of cases	Duration of recording (h)	Number of tachycardias (Number of tachycardias/recording hour)				Number of tachycardias with T wave changes (No./recording hour)	Number of tachycardias with changes of P R interval (No./recording hour)
			Duration <5 min	Duration 5—15 min	Duration >15 min	Total	Total	Total
Full term newborn	50	1248	183 (0.146)	174 (0.139)	46 (0.037)	402 (0.322)	31 (0.077)	21 (0.052)
Healthy premature newborn	30	614	121 (0.197)	53 (0.086)	14 (0.023)	190 (0.310)	41 (0.216)	24 (0.126)
Asphyctic premature newborn	19	129	2 (0.016)	8 (0.062)	4 (0.031)	14 (0.109)	0	0

In the healthy premature group, phasic variation was present in 26 infants (86.6 %). Four of these 26 cases had no variation during the first hours of recording. This normal variation of heart rate was found in 3 asphyctic prematures (30 %), and in one of them it developed only after an 11-hour recording at the age of 19 hours.

There were 11 cases (7 full-term, 3 healthy premature infants and one asphyctic baby) with marked phasic variation. In the scanner display it resembled ectopic arrhythmia so much that this could be excluded only by writing out the recording on paper. In 3 full-term infants the periods of marked phasic variation were longer than 2 hours, but in all other infants the duration of these periods was only a couple of minutes. Marked phasic variation mostly appeared in connection with the lowest basal heart rate levels of 90—130/min, but there were 2 premature infants whose basal heart rates of 143/min were suddenly interrupted by short periods of phasic variation, one of them even had fixed heart rate.

The contrast phenomenon to phasic variation, fixed heart rate [73] was found in 16 infants. All of them were premature ones. The segments of fixed heart rate and normal phasic variation in the premature material are presented in Fig. 10. In 10 of these children, 4 healthy and 6 asphyctic cases, only fixed rate was observed; almost all of them had a history of complicated delivery (2 toxaemias, one maternal uraemia, 2 breech presentations, 3 cases of ablatio placentae, and one retentio placentae partialis). In 2 of them, delivery was by caesarean section. 4 healthy and 2 asphyctic prematures had both fixed rate pattern

and phasic variation in their recordings. There was only one abnormality breech presentation, in this group Maternal hypertension had no relation to the incidence of the fixed heart rate pat tern When the whole group of infants with fixed cardiac rate was taken into consideration, it was found that 12 of them belonged to the birth weight group I (weight below 2000 g) that 10 of them were children of primiparas, and that the mean Apgar score was lower than that of other prematures (6 for the fixed rate group 7 for the others) The difference of the distribu tion of infants with fixed rate between the weight groups I and II is highly significant.

Effect of first feeding on heart rate

The basal heart rates of 24 full term infants representing the hour of first feeding together with one and two hours before and after it are shown in Fig 11 The means of these values are expressed as a heavy curve which has a minimum one hour before the meal, and a maximum one hour after it. Thus, eating produces a rise of basal heart rate but no other changes are found. The difference between the minimum and maximum values of the basal heart rate curve proved to be statistically significant. The first feeding was performed approximately 24 hours after birth in full term infants. The phenomenon was not studied in premature material because of varia tion in the moment of first feeding

Effect of diurnal variation on heart rate

In order to find out whether diurnal variation had any effect on the mean basal heart rate of the material, each recording was divided into 3-hour seg ments according to the time of the day the recording was performed. Thus 8 segments per day were obtained and the mean values of the heart rate of corresponding segments were calculated in the whole material. The values were between 124 and 127/min, the highest values being found during the first three segments of the day (between 00 00 and 09 00). The differences could not be statistically tested, but it can be stated that this distribution does not distort the basal heart rate curve plotted as a function of age

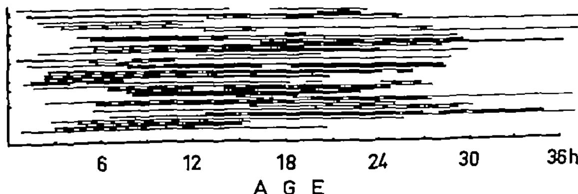


Fig. 10 Segments of phasic variation (light line) and fixed heart rate (heavy line) in the recordings of 40 premature infants. Asphyctic cases have been marked on the vertical axis.

and phasic variation in their recordings. There was only one abnormality breech presentation, in this group Maternal hypertension had no relation to the incidence of the fixed heart rate pattern. When the whole group of infants with fixed cardiac rate was taken into consideration, it was found that 12 of them belonged to the birth weight group I (weight below 2000 g) that 10 of them were children of primiparas, and that the mean Apgar score was lower than that of other prematures (6 for the fixed rate group 7 for the others) The difference of the distribution of infants with fixed rate between the weight groups I and II is highly significant.

Effect of first feeding on heart rate

The basal heart rates of 24 full term infants representing the hour of first feeding together with one and two hours before and after it are shown in Fig 11 The means of these values are expressed as a heavy curve, which has a minimum one hour before the meal, and a maximum one hour after it. Thus, eating produces a rise of basal heart rate but no other changes are found. The difference between the minimum and maximum values of the basal heart rate curve proved to be statistically significant. The first feeding was performed approximately 24 hours after birth in full term infant The phenomenon was not studied in premature material because of variation in the moment of first feedin

Effect of diurnal variation on heart rate

In order to find out whether diurnal variation had any effect on the mean basal heart rate of the material each recording was divided into 3-hour segments according to the time of the day the recording was performed. Thus 8 segments per day were obtained and the mean values of the heart rate of corresponding segments were calculated in the whole material. The values were between 124 and 127/min, the highest values being found during the first three segments of the day (between 00 00 and 09 00) The differences could not be statistically tested, but it can be stated that this distribution does not distort the basal heart rate curve plotted as a function of age.

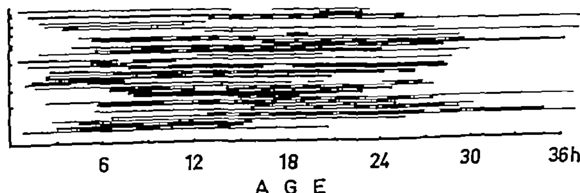


Fig. 10 Segments of phasic variation (light line) and fixed heart rate (heavy line) in the recordings of 40 premature infants. Asphyctic cases have been marked on the vertical axis.

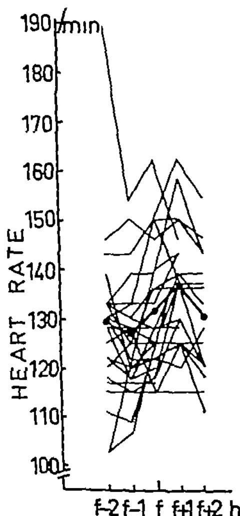


Fig. 11. Basal heart rates of 24 full-term infants during the hour of first feeding (f), and one and two hours before (f — 1, f — 2) and after feeding (f + 1, f + 2). The heavy line represents the mean basal heart rate of the cases.

Discussion

The mean cardiac rate of newborn infants has been reported to be on a uniform level in most conventional ECG studies, as well as in the tape recording investigation of Morgan & Guntheroth [57] as also in the present study. Although, for practical reasons, information concerning the electrocardiographic pattern of the first 30 minutes is lacking in the present investigation, the declining mean basal heart rate during the first 6 hour period is in agreement with the long-term recordings of Desmond et al. [18], and the present results also confirm the slow gradual cardiac acceleration during the period from 6 to 24 hours reported by Contis & Land [12] and Vallbona et al. [100]. On the basis of conventional studies it has been believed that premature infants have a higher heart rate than full term. *No differences were found* in this study between the basal rate levels of term babies and healthy and asphyctic premature babies, but the levels of small premature and large full term newborn were significantly higher than those of infants weighing 2000—3500 g. The *postdelivery dip of the basal rate curve* was more marked in the latter group than in the former. Walsh has also noted that small prematures have significantly higher heart rates [105], but she could not find any difference between those of small and large full-term newborns [106]. The cardiac frequency of distressed infants does not differ from that of normal newborns, although the means of distressed and premature infants are higher than that of full-term [41]. *However mean* heart rates does not appear to have the *same meaning as* basal heart rates: the former is an arithmetic calculation of a couple of pulses, the latter represents the level of existing basic cardiac activity fluctuations from which can be produced by means of various stimuli [10, 29].

The *first* postdelivery cardiac acceleration period [12, 18] was not included into the present study. Tendency to

and phasic variation in their recordings. There was only one abnormality breech presentation, in this group Maternal hypertension had no relation to the incidence of the fixed heart rate pattern. When the whole group of infants with fixed cardiac rate was taken into consideration, it was found that 12 of them belonged to the birth weight group I (weight below 2000 g) that 10 of them were children of primiparas, and that the mean Apgar score was lower than that of other prematures (6 for the fixed rate group 7 for the others) The difference of the distribution of infants with fixed rate between the weight groups I and II is highly significant.

Effect of first feeding on heart rate

The basal heart rates of 24 full term infants representing the hour of first feeding together with one and two hours before and after it are shown in Fig 11 The means of these values are expressed as a heavy curve which has a minimum one hour before the meal, and a maximum one hour after it. Thus, eating produces a rise of basal heart rate but no other changes are found. The difference between the minimum and maximum values of the basal heart rate curve proved to be statistically significant. The first feeding was performed approximately 24 hours after birth in full term infants. The phenomenon was not studied in premature material because of variation in the moment of first feeding.

Effect of diurnal variation on heart rate

In order to find out whether diurnal variation had any effect on the mean basal heart rate of the material, each recording was divided into 3-hour segments according to the time of the day the recording was performed. Thus 8 segments per day were obtained and the mean values of the heart rate of corresponding segments were calculated in the whole material. The values were between 124 and 127/min, the highest values being found during the first three segments of the day (between 00 00 and 09 00) The differences could not be statistically tested, but it can be stated that this distribution does not distort the basal heart rate curve plotted as a function of age

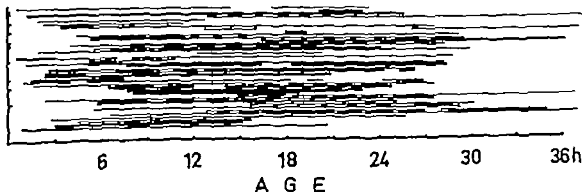


Fig. 10. Segments of phasic variation (light line) and fixed heart rate (heavy line) in the recordings of 40 premature infants. Asphyctic cases have been marked on the vertical axis.

needed. According to the present experiences, a continuous stimulation cannot be produced by volume differ ence originating from early or late clamping of the cord. In the full-term material early clamping of the cord caused a slightly lower mean basal heart rate during the observation period, but the difference was not significant. This is in agreement with the results of conventional recordings [108, 109]

It is also interesting that in the whole material there were 14 per cent of infants with a basal cardiac rate of more than 125/min all the time, and that most of these were prematures. On the other hand, the material included 16 per cent of infants with an exceptionally slow neonatal basal heart rate. Are there sympathicotonic and vagotonic newborn? Is the autonomic tonus related to immaturity or *birth weight* or sex? These *questions* still need *more* investigation.

Although the basal heart rate level of asphyctic infants did not significantly differ from that of healthy prematures, the tendency of asphyctic babies to marked bradycardias, deeper more *frequent, and of longer duration,* is *clearly demonstrated.* The asphyctic group is rather small *for* conclusions, but the results are in agreement with *those of Rudolph et al.* [73] and Urbach et al. [93], where V shaped» short decelerations were found in continuous heart rate recordings of healthy children and bradycardias lasting 30 seconds or more preceded grave asphyxia. A considerable bradycardia and decrease of the aortic blood pressure has also been reported to follow the clamping of the umbilical cord of asphyctic lambs [65].

The phasic variation pattern (sinus arrhythmia, fluctuation of heart rate) was present in all full-term babies from the very beginning. *Most of the prematures also had this variation.* Some *of* the prematures, especially those weighing less than 2000 g, had a tendency to fixed heart rate pattern which has earlier been described by Rudolph et al. [73] Vallbona et al. [100] and Urbach et al. [93] According to these publications and the present results, fixed heart rate is a typical finding *of small, asphyctic prematures* with a history of complicated delivery This pattern may be broken by a grave bradycardia, but it may also be transformed to phasic variation as the child recovers from asphyxia. The tachycardic reactivity of the heart rate to external stimuli is lost in this condition. A common opinion of the cause *of fixed* pattern *is* that the nervous regulation *of* the sinus rhythm *is* eliminated for some reason, *perhaps* by medullary depression. Some of the medullary or other nervous regulatory centres must be still operating, because bradycardias are produced, and according to our clinical observations these bradycardias can be prevented with atropine.

The first feeding had a *fairly* clear *accelerating effect on the* heart rate for an hour or two. The direct *effect* of *feeding*, i.e. the vagal effect of filling *of* the *stomach* described by Phillips et al. [66] in premature infants, could not be demonstrated because of disturbances in the recording. *Like* an *elevated blood* pressure during sucking *[33] the* accelerated heart rate may originate *from* endogenous haemodynamic stimulation, *but more likely* it is caused by the irritating *effect of*

wide fluctuations of heart rate devel oped rapidly in 2—3 hours in the present material, as has been earlier described [18 29] The excursions of the rate deviation of healthy premature infants seem to be lower and disposi tion to maximal tachycardias at first develops more slowly This may be an expression of the slower reactivity of immature infants claimed by Des mond et al. [18] The tachycardic reactivity of asphyctic cases seems to be even more impaired, because the tachycardias never reached the values of healthy premature newborns, and the relative incidence and duration of tachycardias with a frequency of more than 170/min among the asphyctic babies were lower than among the healthy newborns. The limit 170/min was chosen arbitrarily in order to qualify a tachycardic heart rate level differing enough from the basal heart rate area It is known that young children can well tolerate heart rates exceeding 170/min, but it is surprising that a newly born infant can keep his cardiac frequency over this value for many minutes, up to 20 minutes in the premature and up to 60 minutes in the full term material. Peak values of 200/min have been reported for newborn infants [12, 18 47 84 92, 102] Not infrequently this level was exceeded in the present series, where peak values of 260/min for a term infant, and 222/min for a premature one were discovered. Most of the tachycardias occurred in con nection with spontaneous crying, the heart rate pattern being similar to the previous descriptions [18 93] In jections, examinations, and therapeutic procedures were performed much more in the premature, and it is therefore im portant to observe that these disturbing factors do not cause sufficient irri tation to provoke different kinds of heart rate patterns.

In the present series bradycardias of short duration were found in both full term and premature infants. The limit 90/min is empirical because during analysis it was found that short drops below this level were exceptional enough to be collected and studied more closer in the recording and that brady cardias with longer duration fell below this value These very short neonatal bradycardias have been described ear lier [18 48 55 66 93 99 105] They were very common in the premature material of Morgan et al. [55] but were not detected in the comparative investigation of Morgan & Guntheroth concerning full term babies [57] They have been detected following clamping of the umbilical cord, suction of the hypopharynx, defecation, hiccup, yawn, and nasogastric intubation in term in fants [48 99] Phillips et al. produced bradycardias by means of pressing the anterior fontanel, and by ocular and carotid sinus stimulation, and this was also the response of feeding, especially in small prematures [66] In the last mentioned articles these deceleration-acceleration alterations of neonatal heart rate have been supposed to reflect the response of the cardiac pacemaker to stimuli of cardioregulatory centres, which, in turn, are under the control of various detector mechanisms. Thus a special servomechanism for the haemodynamics of newborn infants is formed. Vallbona et al. found no correlation between arterial blood pressure and these heart rate fluctuations [99] It was supposed that volume receptor stimulation produced a cardioinhibitory effect after clamping of the cord, but relatively large volumes would be

ARRHYTHMIAS

Results

Cardiac arrhythmias detected in the material, 50 full term and 40 premature infants, by ECG tape recording are presented in Table VII, and their occurrence during the first 36 hours is shown in Fig. 12.

None of the cases with neonatal arrhythmias had a history of *foetal* cardiac arrhythmias. The distribution of neonatal arrhythmias was equal between the infants of primiparas and multiparas, between the group with maternal hypertension and that of non-hypertensive mothers, and between the full term groups with early and late clamping of the umbilical cord. No significant differences were found between the arrhythmic and non-arrhythmic group in respect to serum calcium and potassium concentrations. The distribution of cardiac irregularities between the three Apgar score groups, 0—3, 4—7 and 8—10 was not equal. In the last two groups there were approximately equal amounts of rhythm disturbances, but no arrhythmias were detected in the first group when the 10 asphyctic prematures were excluded. Nursing procedures had no effect on the regularity of cardiac activation.

The distribution of cases with cardiac arrhythmias in 50 *healthy* newborn infants between 4 birth weight groups is presented in Fig. 13. The columns indicate relative incidences of different arrhythmias. The group with the highest birth weight (IV) included the largest relative number of arrhythmias. Compared with other groups, the difference is highly significant. The supraventricular arrhythmias were distributed equally between the four groups. The same was the case with *nodal beats* in groups I, II, and III.

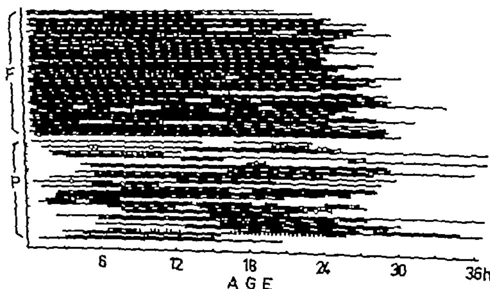


Fig. 12. Occurrence of cardiac arrhythmias, in the recordings of 50 full-term (F) and 40 premature (P) infants. Asphyctic cases have been *marked* on the vertical axis. ✕ sinus arrest, supraventricular arrhythmia, O wandering pacemaker, O nodal rhythms, ~~ ventricular rhythm, — — — supraventricular extrasystoles, and ◆ ventricular extrasystole.

increased motility of the gastrointestinal tract, because most of the infants were very restless and cried for long periods after the first feeding

There was a low positive correlation between the heart rate and rectal temperature at the beginning of recording The temperature was not monitored continuously in the present study but according to Contis & Lind [12] and Desmond et al. [18] the decrease of heart rate and the slight lowering of temperature of the subject are simultaneous phenomena The possible effect of diurnal variation on the basal heart rate was checked. No clear differences between the mean cardiac rates in different time periods of the first day of life could be demonstrated. This calculation could not be tested statistically but it can be said that the values are so equal, that this variation does not disturb the formation of the mean basal heart curve plotted as a function of age. This calculation gives the impression that a newly born infant is haemodynamically rather resistant to the rather feeble external stimuli caused by diurnal rhythm during the first day of life.

Table VII. Number of cases with cardiac arrhythmias in 50 full term, 30 healthy premature, and 10 asphyctic premature newborn infants.

Arrhythmia	Full term	Premature	
		healthy	asphyctic
Sinoatrial block	—	—	1
Supraventricular arrhythmia	6	4	—
Wandering pacemaker	4	—	2
Nodal rhythms	5	2	7
Ventricular rhythm	—	—	3
Supraventricular extrasystoles	3	—	—
Ventricular extrasystoles	1	—	—
Total	19	6	13

ARRHYTHMIAS

Results

Cardiac arrhythmias detected in the material, 50 full-term and 40 premature infants, by ECG tape recording are presented in Table VII, and their occurrence during the first 36 hours is shown in Fig. 12.

None of the cases with neonatal arrhythmias had a history of foetal cardiac arrhythmias. The distribution of neonatal arrhythmias was equal between the infants f primiparas and multiparas, between the group with maternal hypertension and that of non-hypertensive mothers, and between the full-term groups with early and late clamping of the umbilical cord. No significant differences were found between the arrhythmic and non-arrhythmic group in respect to serum calcium and potassium concentrations. The distribution of cardiac irregularities between the three Apgar score groups, 0—3 4—7 and 8—10, was not equal. In the last two groups there were approximately equal amounts of rhythm disturbances, but no arrhythmias were detected in the first group when the 10 asphyctic prematures were excluded. Nursing procedures had no effect on the regularity of cardiac activation

The distribution of cases with cardiac arrhythmias in 50 healthy newborn infants between 4 birth weight groups is presented in Fig 13. The columns indicate relative incidences of different arrhythmias. The group with the highest birth weight (IV) included the largest relative number of arrhythmias. Compared with other groups, the dif ference is highly significant. The supraventricular arrhythmias were distributed equally between the four groups. The same was the case with nodal beats in groups I, II, and III.

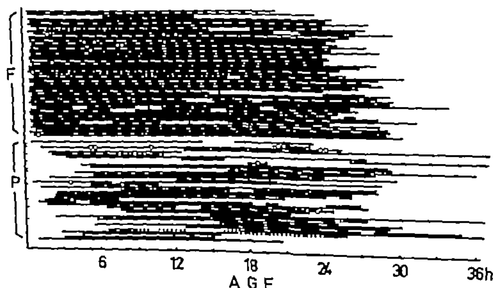


Fig 12 Occurrence of cardiac arrhythmias, in the recordings of 50 full term (F) and 40 prematur (P) infants. Asphyctic cases have been marked on the vertical axis. X sinus arrest, supraventricular arrhythmia, O wandering pacemaker O nodal rhythms, ~ entricular rhythm, ——— supraventricular extrasystoles, and ♦ entricular extrasystole.

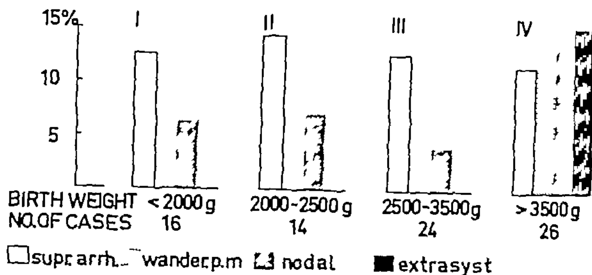


Fig. 13. Relative incidences of cardiac arrhythmias in the four birth weight groups.

Wandering pacemakers and extrasystoles appeared only in group IV. The distribution of the cases with cardiac arrhythmias between the sexes in the healthy full term and premature groups is presented in Table VIII. The supraventricular arrhythmias and nodal beats occurred *mainly in the girls, and* the total number of the girls with rhythm irregularities was also higher than that of the boys. This difference is almost significant. Because of these results, the sex distribution of group IV (birth weight > 3500 g) was checked. The group included 13 boys and 13 girls. Thus the concentration of arrhythmias *in females did not cause the* accumulation of these in the highest birth weight group.

The term supraventricular arrhythmia is not generally used in electrocardiography. This arrhythmia, described by Michaëlsson in newborn infants, consists of a minimal variation of P R duration usually accompanied by a small *fluctuation in the shape* and amplitude of the P wave [54]. In the healthy material, this irregularity appeared in long successions in 10 babies.

An example of wandering pacemaker in a 2 hour-old boy is shown in Fig

Table VIII. Distribution of cardiac arrhythmias between boys and girls in 50 *full term, and 30 healthy premature newborn infants.*

Arrhythmia	Boys		Girls	
	Full term	Premature	Full-term	Premature
Supraventricular arrhythmia	—	1	6	3
Wandering pacemaker	4	—	—	—
Nodal rhythm	—	—	5	2
Supraventricular extrasystole	1	—	2	—
Ventricular extrasystole	1	—	—	—
Total	6	1	13	5
Total material	22	13	28	17

14, where a gradual inversion of P_{V3} with simultaneous prolongation of P R duration is to be seen. This change was reversible. Wandering pacemakers were detected 3 times in one, twice in one, and once in 2 full-term infants during the first 12 hours after birth. During these rapid rhythm alterations the babies were usually reported to be restless.

Nodal rhythm irregularities were detected in 5 full-term and 2 healthy premature infants All of them were girls. In 6 cases, nodal beats occurred in the middle of sinus bradycardia, although in 3 cases only the heart rate fell below 90/min. In one full-term infant a few nodal beats were found at a normal heart rate level. These nodal beats were identical with those described in the report of Morgan et al. with a sudden shortening of P R interval, but without inversion of P deflection [55] Thus, it would be preferable to call this change simple atrio-ventricular (A V) dissociation, to distinguish it from the real nodal rhythms with retrograde atrial conduction found in asphyctic infants.

Supraventricular premature beats were recorded in one full term boy and 2 full-term girls. These arrhythmias were met in long successions during the first 18 hours. An example is presented in Fig 15 Because the ectopic beats had a nearly normal configuration, it was sometimes difficult to identify them in the scanner analysis. The pattern is, however characterized by varying tails of base line in AVSEP display and particularly by a typical irregular sound heard in the loud speaker Only one single ventricular ectopic beat was diagnosed in the whole material. This was just before a wandering pacemaker attack in a 5 hours-old full term boy

In 2 infants, one full-term and one premature, several periods of regular oscillation of base line at a frequency of 800—900/min were established (Fig 16). The amplitude of these minimal

---

In the series of 20 newborn infants examined for the comparison of conventional and tape recordings (section I of this investigation) there was a 3 day-old girl with ventricular premature beats. This arrhythmia was not present in conventional recordings, but it was easily detected in the tape recording (see Fig. 6).

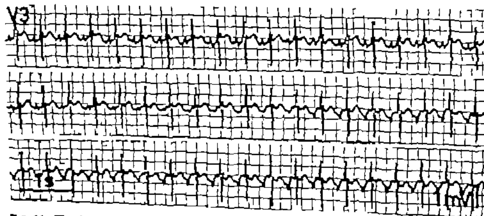


Fig 14. Wandering pacemaker in two-hour full-term boy Electrocardiocharter 550 reproduction.

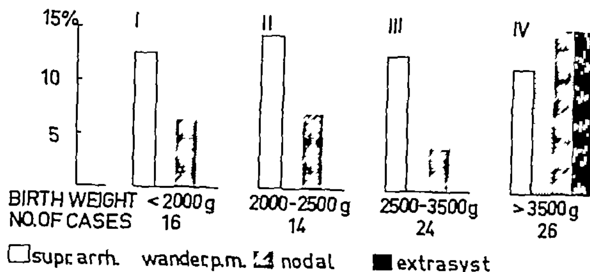


Fig. 13 Relative incidences of cardiac arrhythmias in the four birth weight groups.

Wandering pacemakers and extra systoles appeared only in group IV The distribution of the cases with cardiac arrhythmias between the sexes in the healthy full term and premature groups is presented in Table VIII. The supraventricular arrhythmias and nodal beats occurred mainly in the girls, and the total number of the girls with rhythm irregularities was also higher than that of the boys. This difference is almost significant. Because of these results, the sex distribution of group IV (birth weight > 3500 g) was checked. The group included 13 boys and 13 girls. Thus the concentration of arrhytmias in females did not cause the accumulation of these in the highest birth weight group.

The term supraventricular arrhythmia is not generally used in electrocardiography This arrhythmia, described by Michaëlsson in newborn infants, consists of a minimal variation of P R duration usually accompanied by a *small fluctuation in the shape* and amplitude of the P wave [54] In the healthy material, this irregularity appeared in long successions in 10 babies.

An example of wandering pacemaker in a 2 hour-old boy is shown in Fig

Table VIII. Distribution of cardiac arrhythmias between boys and girls in 50 full term, and 30 healthy premature newborn infants.

Arrhythmia	Boys		Girls	
	Full term	Premature	Full-term	Premature
Supraventricular arrhythmia	—	1	6	3
Wandering pacemaker	4	—	—	—
Nodal rhythms	—	—	5	2
Supraventricular extrasystole	1	—	2	—
Ventricular extrasystole	1	—	—	—
Total	6	1	13	5
Total material	22	13	28	17

14, where a gradual inversion of P_{V3} with simultaneous prolongation of P R duration is to be seen. This change was reversible. Wandering pacemakers were detected 3 times in one, twice in one, and once in 2 full-term infants during the first 12 hours after birth. During these rapid rhythm alterations the babies were usually reported to be restless.

Nodal rhythm irregularities were detected in 5 full-term and 2 healthy premature infants. All of them were girls. In 6 cases, nodal beats occurred in the middle of sinus bradycardia, although in 3 cases only the heart rate fell below 90/min. In one full term infant a few nodal beats were found at a normal heart rate level. These nodal beats were identical with those described in the report of Morgan et al. with a sudden shortening of P-R interval, but without inversion of P deflection [55] Thus, it would be preferable to call this change simple atrio-ventricular (A V) dissociation, to distinguish it from the real nodal rhythms with retrograde atrial conduction found in asphyctic infants.

Supraventricular premature beats were recorded in one full-term boy and 2 full-term girls. These arrhythmias were met in long successions during the first 18 hours. An example is presented in Fig. 15 Because the ectopic beats had a nearly normal configuration, it was sometimes difficult to identify them in the scanner analysis. The pattern is, however characterised by varying tails of base line in AVSEP display and particularly by a typical irregular sound heard in the loud speaker Only one single ventricular ectopic beat was diagnosed in the whole material. This was just before a wandering pacemaker attack in a 5 hours-old full-term boy

In 2 infants, one full term and one premature, several periods of regular oscillation of base line at a frequency of 600—900/min were established (Fig 16) The amplitude of these minimal

---

In the series of 20 newborn infants examined for the comparison of conventional and tape recordings (section I of this investigation), there was a 3 day-old girl with ventricular premature beats. This arrhythmia was not present in conventional recordings, but it was easily detected in the tape recording (see Fig. 6).

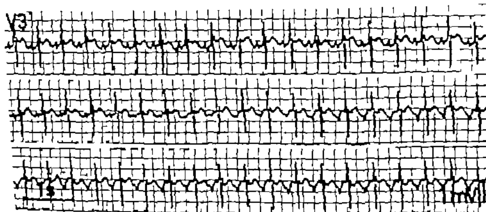


Fig. 14. Wandering pacemaker in two-hour full-term boy. Electrocardiocharter 550 ra

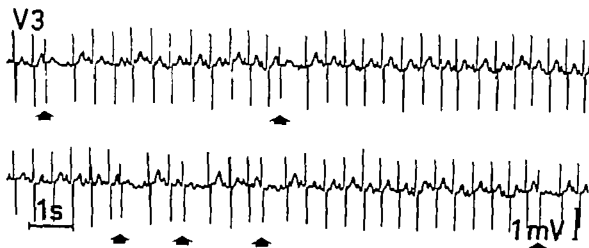


Fig. 15 Supraventricular extrasystoles in a 14 hour full term boy MV 1 reproduction.

serrations changed a little, and they interfered with the reproduction of the P wave. This condition was at first thought to be auricular fibrillation. Because the ventricular rate remained regular without alteration of frequency the phenomenon was considered to be an artifact as in an identical case in the publication of Landtman [35] The origin of this phenomenon remains unclear

The arrhythmias in pathological premature infants will be described in the chapter on asphyctic cases. The conduction disturbances are presented in the chapter dealing with patterns of electrocardiographic intervals

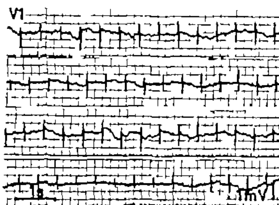


Fig. 16 Oscillating base line, probably artifact, in a 13-hour full term girl. Composite Electocardioscannor 651 reproduction.

Discussion

The results presented here are in contrast to the findings obtained with tape recording technique by Morgan et al. [55] and Morgan & Guntheroth [57] The only real arrhythmia typical of premature newborn infants in these articles was nodal escape during marked sinus bradycardia, and it was not detected *in full term* babies at all. In the present study the incidence of this A V dissociation was highest in the full term infants with a birth weight of more than 3500 g An occasional premature beat was observed in a few infants by Morgan & Guntheroth however in the present recordings, extrasystoles mainly appeared over long periods, except for one ventricular ectopic beat. In the long term ECG study of Vallbona et al 8 cases with sporadic extrasystoles during the first 6 hours after birth were detected in the material of 57 newborn infants [99] It is indeed possible that occasional *ectopic* beats resembling sinus beats can be missed in the scanning

as has been supposed previously [35 65]. The discrepancies mentioned above may be due to the different age distribution and also to the rather small number of arrhythmic cases in the materials.

The total number of infants with real cardiac rhythm irregularities (16 full-term and 7 healthy premature babies), in the material of 60 healthy newborns is, surprisingly of the same magnitude as in the conventional ECG studies of Burghard & Wunnerlich [8] Raihä [67] and Michaëlsson [54] but it is appreciably higher than in most conventional investigations. The same kind of arrhythmias, mostly ectopic pacemakers, have been found by means of conventional ECG as in the present investigation. However most of the premature beats have been ventricular [60 72, 92, 106] whereas they are mainly supraventricular in the present material.

The interesting difference between the sexes has not been found earlier. Although the difference seems to be clear and almost significant ($p < 0.05$) the material and the number of arrhythmias are very low for definitive conclusions.

According to the present investigation, most irregularities are to be found in full term infants, especially in those with high birth weight. In general these disturbances are symptom free, except for restlessness during pacemaker alterations. They do not correlate with obstetric history or with the serum calcium or potassium content of the infant, they do not occur in infants with low Apgar scores. Nursing procedures had no affect on the incidence of arrhythmias. Phillips et al. reported marked sinus depression, P wave changes, and shifting of the pacemaker ensuing from oculobulbar and carotid sinus stimulation, and pressure over the anterior fontanel in premature infants [66]. Occasionally these were associated with apnoeic periods of phasic respiration, although no clear cut relationship between cardiac and spontaneous respiratory irregularities was defined. We did not detect any arrhythmias except sinus bradycardia in association with phasic respiration [15]. Vallbona et al. succeeded in provoking extrasystoles by thumbing the foot in one newly born infant, and in most cases a transient bradycardia was the response to this kind of cutaneous stimulus [99]. Contrary to the report of Phillips et al. [66], feeding did not produce any rhythm irregularities in the present material in the premature, but the ECG corresponding feeding time in full-term babies could not be analysed because of recording disturbances.

Arrhythmias have been considered as evidence of prominent reactivity of the neonatal developing autonomic nervous system [35 68 99]. The vagus sensitizing effect of digitalis, increasing tendency to cardiac rhythm irregularities, has been stressed by Levine & Blumenthal [46]. None of the infants in the present series had received digitalis. In the light of the present investigation, the cardiac arrhythmias described here seem to be a variation of neonatal cardiac action, causing no serious disturbances. If there really are difference between sexes and birth weight groups in the tonus of the autonomic nervous system, investigation of other functions reflecting this tonus during the first days of life is needed.

DURATIONS OF P WAVE, P R, QRS AND Q-T INTERVALS

Results

Duration of P wave

The alterations of mean P wave duration during the first 27 hours in full term and healthy premature infants are presented in Fig 17 The mean values and ranges of both groups at the age of 2 and 24 hours are compared in Table IX. In full term infants the P wave duration was longer than in the premature group during the first 6 hours but this difference was not statistically significant. Generally the P wave duration was of the same magnitude in all the 3 leads, but if different values were detected at the same time the longest of them was chosen for calculations. The same rule was obeyed in the measurement of the other intervals. A gradual shortening occurred during the observation time in both groups, but it was steeper in full term infants. The P wave duration was not dependent on heart rate, but sometimes a minimal shortening was established in association with very high heart rate. This was not a regular response to tachycardia even in the same infant, and the phenomenon is difficult to investigate because of the fusion of P and T waves in high heart frequencies. The time of clamping of the umbilical cord had no effect on P wave duration.

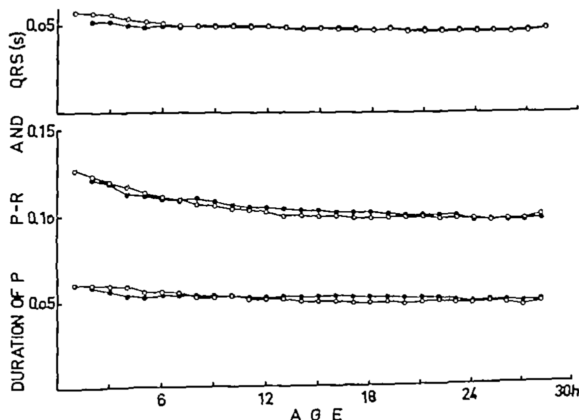


Fig. 17 Mean durations of P wave P R, and QRS intervals during the observation time in 50 full term (O——O) and 30 healthy premature (●——●) infants.

T b l IX. Durations of P wave, P R, QRS and Q-Tc intervals on the 2nd and 24th hours of life in 60 full-term and 30 healthy premature infants. The maximal values found in the 3 chest leads have been taken for calculations.

Material	Age (h)	P duration ( )		P R interval ( )		QRS duration ( )		Q-T ( )	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range
50 full-term	2	0.061	0.03—0.08	0.130	0.09—0.17	0.058	0.05—0.07	0.440	0.37—0.49
30 premature	2	0.060	0.04—0.07	0.122	0.09—0.14	0.053	0.05—0.06	0.442	0.43—0.46
60 full-term	24	0.048	0.03—0.06	0.097	0.08—0.15	0.047	0.04—0.08	0.430	0.37—0.48
30 premature	24	0.049	0.04—0.06	0.097	0.08—0.11	0.047	0.04—0.08	0.443	0.40—0.49

Duration of P R interval

The behaviour of P R interval during the first day of life in full-term and healthy prematures is shown in Fig. 17 and the 2 hour and 24-hour means and ranges for both materials are presented in Table IX. A clear decrease of the duration of this interval is demonstrated in both presentations. This decrease occurred in the material during the first 14 hours. No significant differences could be noted between the values of full term and healthy premature infants, and between those of the 4 birth weight groups. The values of the group with early clamped umbilical cords were lower than those of late clamped during the whole observation period. This difference proved to be statistically significant during the first 4 hours of life. Later the values of the early and late clamped groups were more equal. When the curves of P wave duration and P R interval duration are compared in Fig 17 the prolongation of P R interval seems to be caused by the prolongation of P R segment and not by that of P wave duration.

The maximal duration of P R interval was 0.18 s in a full-term infant during the first hour of life. If values of 0.14 s or more are regarded as criteria of first degree A V block as in the study of Morgan et al. [35] there were 11 such cases in the full-term material, and 3 in the premature group, all of whom were healthy But in all of these 14 infants, a shortening of P R interval below 0.14 s occurred during the recording time. The only real A V block in the whole material was a reversible 2 1 A V block during an asphyctic bradycardia in a 24 hour-old premature boy

A minimal shortening of 0 01 s was sometimes, but not constantly found in association with tachycardia of more than 170/min. The incidence of tachy cardias with shortening of P R interval among all the tachycardias, was approximately 5 per cent in full term, and 13 per cent in healthy premature groups (Table VI) These changes were not detected in connection with every tachycardia of the same degree in the same infant. No linear relationship could be generally demonstrated between P R interval duration and heart rate.

Duration of QRS interval

Curves of mean QRS intervals for full term and healthy premature new borns are presented in Fig 17 and the 2 hour and 24-hour values are compared in Table IX. It can be seen that this interval too shortened in both groups during the 6 hours after birth, and shortening was more prominent in the full term group However no sta tistically significant differences between the values of full term and healthy prematures could be demon strated. The infants with late clamped umbilical cords had significantly longer QRS duration during the first 2 hours than those with early clamped cords. The heart rate had no effect on the QRS interval No abrupt alterations of this interval could be detected during the ECG recordings except in terminal asphyxia.

In two full term boys the duration of the QRS interval was 0 07 s in the first hour of life and the R_{V1} wave was notched. Thus an incomplete right bundle branch block configuration was formed. However the QRS interval shortened later to 0 05 s, and the notching of the R_{V1} became less marked, as can be seen in Fig 18 Thus it is questionable whether it is at all justi fied to call this extremely prolongated QRS a RBBB QRS intervals of 0 07 s were found in 4 additional infants during the first hour of life but in these cases no notching of the R wave was present. In the present recording the QRS of premature infants was never longer than 0 06 s, but the longest

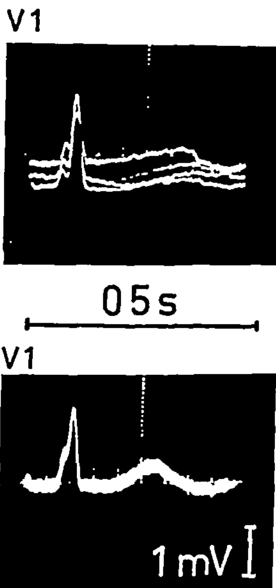


Fig. 18. The decrease of QRS duration, and notching of R wave during the first hours of life in a full term boy The upper record ing at the age of 30 min, the lower at the age of 4 h.

intervals were detected during the first hours of life, and these values were lacking in many premature babies.

Duration of Q-T interval

Because the duration of the Q-T interval is very sensitive to heart rate alterations, this *effect of heart rate was eliminated in the* classical manner by correcting the Q-T interval according to Barett's formula $\text{Q-Tc} = \frac{\text{Q-T measured}}{\sqrt{\text{cycle lenght}}}$ [6] The 2-hour and 24-hour values of Q-Tc are shown in Table IX. The Q-Tc values of full-term and healthy premature infants were practically *equal during the first 5 hours*, but from the 6th hour of life, the mean values of healthy prematures were significantly higher than those of full term babies, the difference being of the same magnitude as that given in Table IX for the age of 24 hours. A transitive prolongation of Q-Tc occurred during the 3rd—6th hours of life. the mean Q-Tc was 0 44 s in the 2nd hour in both groups *of infants*, the value of 0.448 s was achieved in the full term, and that of 0 452 s in premature in the 4th hour The mean value of the full-term material gradually decreased until the stable level of 0.43 s was reached. The maximal mean Q-Tc values were achieved in the 6th—7th hours in the *premature group*, and *thereafter the values remained* on the statistically significantly higher level of 0.445—0 45 s. The Q-Tc curves for the 4 birth weight groups are presented in Fig 19 The values of groups I, II, and III were significantly higher than those of group IV during the whole observation time. *No relationship* between the alterations of the Q-Tc and the other intervals appeared to be present.

The moment of cord clamping produced no effect on the Q-Tc interval. No linear relationship was detected between the durations of P wave, P R interval, QRS interval, and Q-Tc, and the Apgar score, maternal *hypertension* or the parameters listed in Table IV



Fig. 19 Mean Q-T values of healthy infants with birth weight of (I) < 2000 g, (II) 2000—2500 g, (III) 2500—3500 g, and (IV) > 3500 g.

In cases with hyperpotassaemia (serum potassium more than 7 mEq/l) no prolongations of P wave duration, P R interval, or QRS interval were found, except in one full term girl with a serum potassium of 7 4 mEq/l who had a P wave duration of 0 08 s and P R interval of 0 18 s, but the other intervals were normal. There were still more elevated serum potassium concentrations, up to 8.9 mEq/l without prolongated intervals, at the beginning of the recording in premature infants. The slightly elevated serum calcium concentration up to 13 1 mg/100 ml had no effect on the Q-Tc. No correlation was established between the rectal temperature at the beginning of the recording, and the initial Q-Tc value.

Discussion

The results concerning means, and ranges of duration of P wave, and P R interval, are in agreement with the results obtained on the first day of life with conventional ECG technique in full term and premature infants, although the measurements were made in standard lead II in these publications [14 20 22 24 42, 54 69 72, 101 102, 112] The initial prolongation of these intervals has been reported by Michaëlsson [54] Walsh [102] and Jagielski et al. [39] but the present study proves that gradual shortening of P wave and particularly of P R interval, take place during the first 14 hours after birth. There are significant differences between the P R and QRS intervals of the groups with early and late clamping of the cord, during the first hours, which is in agreement with the results of Walsh [108 109] However contrary to the results of Walsh, no difference exists between the corresponding values of P wave duration. A discrepancy also exists between the reports of Walsh [102, 108, 109] and the present results, concerning the role of P wave duration in prolongation of the P R interval.

As possible causes for the prolongation of these intervals, left atrial hypertrophy or dilatation, vagal tone and volume load of the heart have been proposed [102 108 109] Elevated serum potassium content has also been held responsible for prolongation of P and P R interval durations [58] In the present series, there was only one case with extreme prolongation of these segments, associated with moderate hyperpotassaemia. An increase in vagal activity has been reported to result from volume loading of the atria [84] At the present time we do not know whether these atrial reflexes are mature in newborn infants, but it is possible that the more prominent prolongation of the P R interval, compared with that of P wave duration, may be of vagal origin. The question of whether the stimulus of vagal tone is volume load of the left atrium, resulting from adjustments of the neonatal pulmonary circulation, still remains unresolved.

Contradictory reports concerning the relationship between heart rate, and durations of P wave, and P R interval, have been presented [3 23 102, 112] According to the present observations, shortening of these intervals may occur quite randomly in association with tachycardias, reflecting perhaps, the alternating control of the autonomic nervous system upon the electric activation of the heart.

The means and ranges of QRS duration, are equal to the values of conven

tional investigations [20 22, 24, 84, 69 72] A significant difference between the longer QRS interval, of infants less than 30 min old, and the shorter one of infants more than 4 hours old, has been described by Walsh [102] According to the present study the shortening of the QRS interval takes place during the first 12 hours, it is most prominent during the first 6 hours, and the decrease is steeper in full-term infants, although there are no significant differences between the values of full-term and premature babies. The changes are fairly similar to those of the P wave and P-R interval durations. The same regulating factors have been discussed as being responsible for shortenings of all these intervals, by Walsh, who has also found that no dependence exists between the decrease of the QRS interval, and that of heart volume in roentgenograms [103] The present results offer no more information concerning the etiology of these alterations of the QRS interval.

The present values of Q-Tc are longer than those of Craige & Harned [14] but equal to those of Walsh [103] and Fonseca Costa et al [22]. This may be due to the difficulty of measuring the Q-T interval exactly The present results confirm the observation of Walsh, concerning the non-dependence between the changes of Q-Tc, and those of the durations of the P wave, P R, and QRS intervals [103] The maximal Q-Tc values are found simultaneously with the lowest basal heart rates. Significant differences were found between the Q-Tc values of small and large premature, and full-term groups. In the comparison of the birth weight groups, shorter Q-Tc values correspond to higher basal heart rates, but these phenomena are not parallel in relation to time. Hypothermia produces a prolongation of Q-T interval [79] In the present investigation there was a low positive correlation between the initial basal heart rate, and the rectal temperature, measured at the beginning of the recording, but no correlation was found between the temperature and Q-Tc. Significantly longer Q-Tc intervals developed in the premature group, and in general, premature infants tend to be thermolabile. According to the present study the maximal Q-Tc values appeared at the age of 3—6 hours in the full-term, and 6—7 hours in the premature group. However the body temperature has been shown to have a minimum during the first 5—345 minutes post partum [12, 18, 40] Thus the explanation of the postnatal behaviour of Q-Tc remains an open question in the light of the present study

In cases with hyperpotassaemia (serum potassium more than 7 mEq/l) no prolongations of P wave duration, P R interval, or QRS interval were found, except in one full term girl with a serum potassium of 7 4 mEq/l who had a P wave duration of 0 08 s and P R interval of 0 18 s, but the other intervals were normal. There were still more elevated serum potassium concen trations, up to 8.9 mEq/l without prolongated intervals, at the beginning of the recording in premature infants. The slightly elevated serum calcium concentration up to 13 1 mg/100 ml, had no effect on the Q-Tc. No corre- lation was established between the rectal temperature at the beginning of the recording and the initial Q-Tc value.

Discussion

The results concerning means, and ranges of duration of P wave, and P R interval, are in agreement with the results obtained on the first day of life with conventional ECG technique in full term and premature infants, al though the measurements were made in standard lead II in these publications [14, 20 22, 24 42, 54, 69 72 101 102, 112] The initial prolongation of these intervals has been reported by Mic haelsson [54] Walsh [102] and Ja gielski et al. [39] but the present study proves that gradual shortening of P wave, and particularly of P R interval, take place during the first 14 hours after birth. There are sig nificant differences between the P R and QRS intervals of the groups with early and late clamping of the cord, during the first hours, which is in agreement with the results of Walsh [108 109] However contrary to the results of Walsh, no difference exists between the corresponding values of P wave duration. A discrepancy also exists between the reports of Walsh [102, 108 109] and the present results, concerning the role of P wave duration in prolon- gation of the P R interval.

As possible causes for the prolon gation of these intervals, left atrial hypertrophy or dilatation, vagal tone, and volume load of the heart have been proposed [102, 108 109] Elevated serum potassium content has also been held responsible for prolongation of P and P R interval durations [58] In the present series, there was only one case with extreme prolongation of these segments, associated with mod- erate hyperpotassaemia. An increase in vagal activity has been reported to result from volume loading of the atria [64] At the present time, we do not know whether these atrial reflexes are mature in newborn infants, but it is possible that the more prominent prolongation of the P R interval, compared with that of P wave duration, may be of vagal origin. The question of whether the stimulus of vagal tone is volume load of the left atrium, resulting from adjustments of the neonatal pulmonary circulation, still remains unresolved.

Contradictory reports concerning the relationship between heart rate, and durations of P wave and P R interval, have been presented [3 23, 102, 112] According to the present observations, shortening of these intervals may occur quite randomly in association with tachycardias, reflecting perhaps, the alternating control of the autonomic nervous system upon the electric acti vation of the heart.

The means and ranges of QRS dura tion, are equal to the values of conven

tional investigations [19, 22, 24, 54, 69 72] A significant difference between the longer QRS interval, of infants less than 30 min old, and the shorter one of infants more than 4 hours old, has been described by Walsh [103]. According to the present study the shortening of the QRS interval takes place during the first 12 hours, it is most prominent during the first 6 hours, and the decrease is steeper in full-term infants, although there are no significant differences between the values of full term and premature babies. The changes are *fairly similar to* those of the P wave and P R interval durations. The same regulating factors have been discussed as being responsible for shortenings of all these intervals, by Walsh, who has also found that no dependence exists between the decrease of the QRS interval, and that of heart volume in roentgenograms [103]. The present results offer no more information concerning the etiology of these alterations of the QRS interval.

The present values of Q-Tc are longer than those of Craige & Harned [14], but equal to those of Walsh [103] and Fonseca Costa et al [22]. This may be due to the difficulty of measuring the Q-T interval exactly The present results confirm the observation of Walsh, concerning the non-dependence between the changes of *Q-Tc, and those* of the durations of the P wave, P R, and QRS intervals [103] The maximal Q-Tc values are found simultaneously with the lowest basal heart rates. Significant differences were found between the Q-Tc values of small and large premature, and full-term groups. In the comparison of the birth weight groups, *shorter Q-Tc values correspond* to higher basal heart rates, but these phenomena *are not parallel in relation* to time. Hypothermia produces a prolongation of Q-T interval [79] In the present investigation there was a low positive correlation between the initial *basal heart rate*, and the *rectal temperature*, measured at the beginning of *the recording, but no correlation was* found between the temperature and Q-Tc. Significantly longer Q-Tc intervals developed in the premature group, and in general, premature infants tend to be thermolabile. According to the present study the maximal Q-Tc values appeared at the age of 3—6 hours in the full-term, and 6—7 hours in the *premature group. However* the body temperature has been shown *to have* a *minimum during* the first 5—345 minutes post partum [12, 18, 40]. Thus the *explanation* of the postnatal behaviour of Q-Tc remains an open question in the light of the present study

In cases with hyperpotassaemia (serum potassium more than 7 mEq/l) no prolongations of P wave duration, P R interval, or QRS interval were found, except in one full term girl with a serum potassium of 7 4 mEq/l who had a P wave duration of 0 08 s and P R interval of 0 18 s, but the other intervals were normal. There were still more elevated serum potassium concen trations, up to 8.9 mEq/l without prolongated intervals, at the beginning of the recording in premature infants. The slightly elevated serum calcium concentration up to 13 1 mg/100 ml, had no effect on the Q-Tc. No corre-lation was established between the rectal temperature at the beginning of the recording and the initial Q-Tc value.

Discussion

The results concerning means, and ranges of duration of P wave and P R interval, are in agreement with the results obtained on the first day of life with conventional ECG technique in full term and premature infants, al though the measurements were made in standard lead II in these publications [14 20 22, 24 42 54 69 72, 101 102 112] The initial prolongation of these intervals has been reported by Mic-haëlsson [54] Walsh [102] and Ja gielski et al. [39] but the present study proves that gradual shortening of P wave and particularly of P R interval, take place during the first 14 hours after birth. There are sig nificant differences between the P R and QRS intervals of the groups with early and late clamping of the cord, during the first hours, which is in agreement with the results of Walsh [108 109] However contrary to the results of Walsh, no difference exists between the corresponding values of P wave duration. A discrepancy also exists between the reports of Walsh [102, 108 109] and the present results, concerning the role of P wave duration in prolon gation of the P R interval

As possible causes for the prolon gation of these intervals, left atrial hypertrophy or dilatation, vagal tone and volume load of the heart have been proposed [102 108 109] Elevated serum potassium content has also been held responsible for prolongation of P and P R interval durations [58] In the present series, there was only one case with extreme prolongation of these segments, associated with mod erate hyperpotassaemia. An increase in vagal activity has been reported to result from volume loading of the atria [64] At the present time we do not know whether these atrial reflexes are mature in newborn infants, but it is possible that the more prominent prolongation of the P R interval, compared with that of P wave duration, may be of vagal origin. The question of whether the stimulus of vagal tone is volume load of the left atrium, resulting from adjustments of the neonatal pulmonary circulation, still remains unresolved.

Contradictory reports concerning the relationship between heart rate, and durations of P wave, and P R interval, have been presented [3 23 102, 112] According to the present observations, shortening of these intervals may occur quite randomly in association with tachycardias, reflecting perhaps, the alternating control of the autonomic nervous system upon the electric acti vation of the heart.

The means and ranges of QRS dura tion, are equal to the values of conven

tional investigations [20, 22, 24, 54, 69 72] A significant difference between the longer QRS interval, of infants less than 30 min old, and the shorter one of infants more than 4 hours old, has been described by Walsh [103] According to the present study the shortening of the QRS interval takes place during the first 12 hours, it is most prominent during the first 6 hours, and the decrease is steeper in full-term infants, although there are no significant differences between the values of full-term and premature babies. The changes are fairly similar to those of the P wave and P R interval durations. The same regulating factors have been discussed as being responsible for shortenings of all these intervals, by Walsh, who has also found that no dependence exists between the decrease of the QRS interval, and that of heart volume in roentgenograms [103]. The present results offer no more information concerning the etiology of these alterations of the QRS interval.

The present values of Q-Tc are longer than those of Craige & Harned [14] but equal to those of Walsh [103] and Fonseca Costa et al [22]. This may be due to the difficulty of measuring the Q-T interval exactly The present results confirm the observation of Walsh, concerning the non-dependence between the changes of Q-Tc, and those of the durations of the P wave, P-R, and QRS intervals [103] The maximal Q-Tc values are found simultaneously with the lowest basal heart rates. Significant differences were found between the Q-Tc values of small and large premature, and full-term groups. In the comparison of the birth weight groups, shorter Q-Tc values correspond to higher basal heart rates, but these phenomena are not parallel in relation to time. Hypothermia produces a prolongation of Q-T interval [79] In the present investigation there was a low positive correlation between the initial basal heart rate, and the rectal temperature, measured at the beginning of the recording, but no correlation was found between the temperature and Q-Tc. Significantly longer Q-Tc intervals developed in the premature group, and in general, premature infants tend to be thermolabile. According to the present study the maximal Q-Tc values appeared at the age of 3—6 hours in the full-term, and 6—7 hours in the premature group. However the body temperature has been shown to have a minimum during the first 5—345 minutes post partum [12, 18, 40] Thus the explanation of the postnatal behaviour of Q-Tc remains an open question in the light of the present study

Table X. Means and ranges of P, R, S and T wave voltages at the age of 2 and 24 hours in 50 full term and 30 healthy premature infants.

P wave (initial/terminal deflection)

		V 1		V 3		V 5	
Material	Age (h)	mean (mV)	range (mV)	mean (mV)	range (mV)	mean (mV)	range (mV)
Full term	2	0.13/—0.06	0.05—0.20/—0.05— —0.10	0.19	0.10—0.40	0.14	0.05—0.30
	24	0.14/—0.06	0.05—0.20/—0.05— —0.10	0.19	0.10—0.30	0.13	0.05—0.20
Premature	2	0.14/—0.06	0.05—0.20/—0.05— —0.10	0.13	0.05—0.30	0.15	0.05—0.30
	24	0.11/—0.07	0.05—0.20/—0.05— —0.10	0.11	0.05—0.20	0.11	0.05—0.20

R wave

Full term	2	1.33	0.80—1.90	1.45	0.60—2.30	0.91	0.10—1.50
	24	1.26	0.60—1.90	1.35	0.60—2.00	0.87	0.10—1.30
Premature	2	1.08	0.70—1.50	1.23	0.50—2.00	1.07	0.40—1.90
	24	0.88	0.50—1.40	0.88	0.40—1.40	0.62	0.20—1.00

S wave

Full term	2	0.56	0.10—1.20	1.48	0.80—2.00	1.22	0.20—1.70
	24	0.57	0.10—1.30	1.49	0.90—1.90	1.22	0.20—1.70
Premature	2	0.67	0.10—1.20	1.22	0.40—1.80	0.80	0.60—1.10
	24	0.62	0.10—1.30	1.12	0.90—1.50	0.57	0.20—0.90

T wave (initial/terminal deflection)

Full term	2	0.22/—	—0.10—0.50/—	0.26/—0.06	—0.20—0.70/—0.10—0.10	0.16/—	—0.2—0.6/—
	24	0.33/—	0.10—0.70/—	0.21/0.10	—0.40—0.90/0.10	—0.01/—0.10	—0.4—0.4/—0.10
Premature	2	0.12/—	—0.20—0.30/—	—0.01/0.10	—0.40—0.40/0.10	0.06/—0.10	—0.2—0.2/—0.10
	24	—0.02/—	—0.40—0.40/—	—0.15/0.00	—0.60—0.10/—0.10—0.10	—0.02/—0.10	—0.3—0.2/—0.10

VOLTAGE PATTERNS

Results

P wave

The means and ranges of the P wave in the V1, V3, and V5 leads, for the 2nd and 24th hours of life, are given in Table X. The P_{V1} was mostly diphasic, with an initial positive, and a terminal negative deflection. The P_{V3} was always positive, and usually notched. The calculations were made according to the higher peak of the P_{V3} wave. The P_{V5} was always a round, very seldom notched, upright deflection. The shape, and magnitude of the P wave remained stable in all leads during the observation period. Generally the mean P wave values of the full term group were higher than those of the premature group, but this difference was not statistically significant. The moment of clamping of the umbilical cord had no effect on the P wave configuration or magnitude. Besides the minimal fluctuation of the P wave voltage in supraventricular arrhythmia, and clear alterations of this atrial deflection in cases of wandering pacemaker variations of its shape and size were detected during tachycardias. It usually took the form of a round or notched P wave, turned reversibly into a peaked one, with a simultaneous increase of voltage. Less frequently a normal P wave became notched during tachycardia. These alterations were more common in full-term infants, but the exact incidences will not be given, for these tachycardic P wave alterations are difficult to estimate, due to the fusion of P and T or U waves.

QRS complex

The configuration types of the QRS complex at the beginning of the tape recording are presented in Fig. 20 where the mean voltages and the incidences of these types are also shown. These data reflect a typical neonatal right ventricular preponderance, but electrocardiographic configuration, pe-

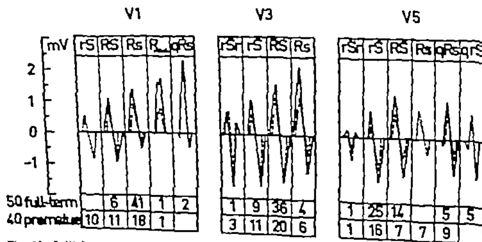


Fig. 20. Initial morphology and mean voltage of QRS complex in 50 full-term (continuous line) and 40 premature infants (interrupted line). The numerical incidences are marked under the corresponding voltage patterns.

culiar to left ventricular dominance, is also found, especially in the premature group In 3 cases, only a large, notched, R wave formed the whole ventricular depolarization complex, without S wave. An exceptional rSr pattern may be formed from rS pattern, followed by a giant post-S spike, and may therefore, be an artifact.

The Q_{V1} wave appeared with a voltage of 0 1 mV initially in 2 full term, and one premature infant, and was not met later in the recording in either of these full term babies. No Q wave was present in the V3 lead. Q_{V5} was found in 10 full term, and 9 premature infants. Its initial means are given in Fig 20 the range being 0 1—0.5 mV in the full term and 0 1—0.2 mV in the premature infants. The voltages of Q waves remained stable during the observation time and no significant differences were detected between the values of the full term and premature material although the incidences of Q wave were very small for statistical calculations.

The 2 hour and 24-hour means and ranges of R and S waves, for both full term and premature materials, are presented in Table X. To make the material suitable for comparison, the voltages of R and S in the three chest leads were studied in 3-hour segments, after the first hour of life. As the voltages of R and S were followed, it was found that in all three chest leads a minimal decrease of amplitude of R wave occurred in the full term group, and a more marked one in the healthy premature group, whereas the S waves behaved in different ways in different leads and groups. A minimal increase of S_{V1} amplitude was found in both groups during the first 28 hours of life. The S_{V3} and S_{V5} voltages remained constant in the full term group but a slight decrease of the S_{V3} voltage, and a clear increase of S_{V5} voltage, were established in the prematures. In the V1 lead, the R wave voltage of the full term group was, permanently highly significantly higher than that of the prematures, but no difference existed between the corresponding S waves. In the V3 lead, both the R and S wave amplitudes of the full term babies were highly significantly higher than those of the premature group. Significant differences could be demonstrated between the R wave voltages of the full term and premature groups in the V5 lead, and the differences between the higher S_{V5} values of the full term, and the lower ones of the premature proved to be highly significant.

The behaviour of the resulting mean R/S ratio in the three chest leads is presented in Fig 21 Declining R/S_{V1} curves were found in both full term and healthy premature infants, but the difference between the curves did not prove to be significant. No changes appeared in the R/S ratio in the V3 lead. The R/S_{V5} of the full term babies remained rather stable, but a clear decrease in that of the prematures occurred during the observation time. The difference between the R/S_{V5} values of both groups was significant between the ages of 2—13 hours.

Thus, the neonatal electric right ventricular preponderance is demonstrable also by ECG tape recording According to the present results, it decreases during the first hours of life, in both full term, and healthy premature infants. The behaviour of the R/S_{V5} ratio gives an impression of diminution of electric forces reflecting the left ventricular depolarization of

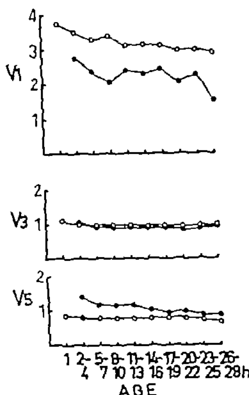


Fig. 21. Behaviour of R/S ratio in V1, V3, and V5 leads in the tape recordings of 60 healthy full-term (O——O), and 30 healthy premature infants (●——●). The values have been calculated for 3-hour periods after the initial first-hour readings.

the premature group, in contrast to that of the full-term infants. The voltages of R and S were significantly higher in the full-term infants than in the prematures, in all leads, except the voltage of S_{V1} where no differences could be demonstrated.

No abrupt voltage alterations in these deflections were detected in the recordings, with the exception of drastic QRS d formations in terminal asphyxia.

Ventricula epolarization

S-T depressions, with an approximate magnitude of 0.1 mV (range —0.1 — —0.2 mV), were found in 8 full-term, and 1 premature infant $S\text{-}T_{V3}$ deviations of the same magnitude (range —0.1 — + 0.2 mV), in 5 full-term infants, and depressions of 0.1 mV in 4 prematures. $S\text{-}T_{V3}$ elevations of approximately 0.15 mV (range + 0.1 — + 0.3 mV), appeared in 22 infants of the full term group, and of 0.1 mV (range + 0.1 — + 0.2 mV), in 10 premature babies. An $S\text{-}T_{V3}$ *depression of 0.1* mV was present in one premature infant. Most of the S-T deviations were junctional, and generally developed and disappeared *gradually over* a couple of hours, only few (2 in V1 3 in V3, and 8 in V5 in the full term, none in premature infants) were present during the whole recording, and all except 4 were asymptomatic. Their behaviour in relation to the observation time, was not *uniform* at *all*. Because *of* the unclear reproduction of the S-T segment in the present tape recordings, (page 27) and the insufficient data concerning *body movements of subjects* in the present material, it is hardly possible to make conclusions about the changes of *S-T* segments as a function of time, in respect to the present investigation.

Rapid S-T alterations were detected *in 4 full-term infants*. Three of them occurred in association with moderate tachycardia, a 16-hour boy reported to have minimal grunting, had a reversible disappearance *of* 0.2 mV $S\text{-}T_{V1}$ depression, accompanied by T wave inversion, a 21-hour girl, reported *crying, had* a reversible 0.1 mV depression of $S\text{-}T_{V1}$, accompanied by T wave inversion, and a 27 hour girl, crying, had a disappearance of 0.2 mV $S\text{-}T_{V3}$ depression, *followed* by a reversible 0.1 mV depression after the tachycardia, and then a gradual restoration of the *original* 0.2 mV depression. The

4th case, a 10-hour boy was reported to be restless, and during this time a sudden prominent nonjunctional S-T_{V3} depression was established (Fig 22) which disappeared in a couple of minutes, and was not met with later in the recording No rapid S-T changes were detected in the premature group, even in the asphyctic cases, except in the grotesquely deformed ECG of the dying heart.

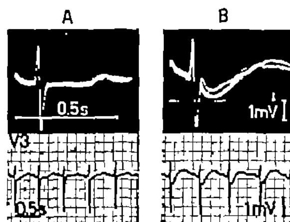


Fig. 22. Electrocardioscanner (upper) and Electrocardiocharter (lower) reproductions of basal ECG pattern (A) and marked S-T depression (B) in V3 lead in a 10-hour full term boy

The 2 hour and 24-hour means and ranges of the T wave amplitudes in the three chest leads are given in Table X, and the alterations of the mean T wave voltages of the full term, and healthy premature infants, during the first 27 hours, are presented in Fig 23. During the first 6 hours, the voltage of the T wave in the V1 lead gradually gained in the full term group, whereas in the same period, a gradual diminution of the T wave occurred in the prematures. There was a significant difference between the values of both groups after the 5th hour of life. The same was the case between the T_{V3} voltages of the full term, and

Fig. 23. Behaviour of mean T wave voltages in V1 V3 and V5 leads in the tape recordings of 50 full term (O——O) and 30 healthy premature infants (●——●) during the observation period.

healthy premature groups. In many cases, the difference was highly significant. The T_{V3} values of the full-term tended to remain permanently positive, but those of the premature had a tendency to inversion after the first hours of life. In the V5 lead, the T deflections of the full-term were at first mainly upright but became inverted after the 3rd hour of life. Afterwords, however they again became more and more positive. The same tendency was present in the corresponding values of the prematures, but the wandering of the mean T_{V1} curve fails to demonstrate the phenomenon well, because of the scattering of the values.

All the T_{V1} deflections were monophasic, and mainly asymmetric, as has been described in conventional ECG by Sodi-Pallares et al. [84]. There were 7 full-term, and 5 premature infants, with a diphasic T_{V3} at some time during the recording, the initial main part of which was used for the calculations for Fig. 23. The same was the case in the T_{V3} waves, which were diphasic in 4 full term and 3 premature babies. The terminal deflection was usually lower than 0.1 mV only one full-term infant having an amplitude of 0.2 mV in the terminal part of the T_{V1}. No statistical differences were found between the terminal T wave parts of the full term and premature groups, but the incidence was very small in the material

The only rapid changes of T waves were those noted in association with tachycardias, an example of which is shown in Fig. 24. In most cases, this change was a flattening of the T wave, negative or positive, after a marked heart rate acceleration. The number of these changes in connection with tachycardias with a rate of more than 170/min, has been given in Table VI, but there were 4 more in the full-term infants, and 2 in the prematures, following a tachycardia with a lower rate. The degree of these T wave flattenings was not proportional to the heart rate acceleration, or the duration of the tachycardia. They were not found constantly with the same cardiac rates, even in the same infant. They were not detected in the asphyctic group. Three full term infants had a T wave inversion during a tachycardia, 2 of them being accompanied by changes of the S-T segment.

V3



0.5s



Fig. 24. Flattening of T_{V3} wave after tachycardia in 12-hour full-term boy demonstrated in Electrocardioscanner display

U waves with an amplitude of up to 0 1 mV were detected in leads V3 and V5 U_{V3} was present in 6 full term and 4 premature infants, and U_{V5} in 10 full term, and 2 premature in fants. The majority appeared during the first hours after birth, but their inci dence is too small for statistical calcu lations. Appearance or disappearance of a U wave in some lead was not related to changes in other deflections.

Discussion

The present results of P wave ampli tude are in agreement with the con ventional ECG studies of Ziegler and Michaëlsson, but the voltages are in general, a little higher [112,54] This is also to be expected, because no significant differences could be demonstrated between the P wave reproductability of the conventional and tape recordings in section I of this investigation. Peaked right precordial P waves have been presumed by Thaon (91) Vanoni (101) and Emmanouilides et al (20) to result from high pulmonary arterial pressure and right atrial overload. No uniform changes in the P wave amplitudes could be found in the present series, but pressure alterations also occur gradually after birth [21 65] The early clamping of the cord has been reported to produce lower P_{II} voltage [108] but no effect on the precordial P waves could be established in the present study The transformation of P waves during tachycardias is in agreement with the hypothesis of atrial volume load, but no prolongation of P wave duration was present during these tachycardic P wave alterations.

The voltage values of the QRS complex cannot be compared directly with those obtained by means of convention al recording technique, and the ampli tude variations recorded must be consi dered with reservation, because of the attenuated voltage repeating capability of the equipment, and because of the possibilities of unhomogenous magnetic tape, and change in the subject s position.

The appearance of Q waves in the V1 and V5 leads is in agreement with the conventional studies [20 76 104, 110 112] Rarely the Q wave has been found on the right precordium, and this has been held to reflect right ventricu lar hypertrophy [58]

The magnitude of the present values for R and S deflections, are nearly the same as those in the corresponding conventional studies [17 20 76 104 105 110 112] when the present values are corrected according to the diagrams of Fig 5 The R/S ratios are quite different because of the restricted S wave reproduction in the tape recording devices. Decreasing R wave amplitudes in the right and mid precordial chest leads after the first hour of life have been described by Walsh, and the same was the case with left precordial S waves [104] The present results resem ble the observations concerning R waves, but no alterations of the S_{V1} wave were detected, except in the premature group. The changes in R/S ratios indicate diminution of the right ventricular electric dominance during the first day of life in both full term, and premature infants, but there is also a decrease of left ventricular forces in the premature group. A low R/S ratio in the right precordial leads has been found in association with a left to-right shunt via the ductus arteriosus, and a high R/S

ratio in left precordial leads with a lower pulmonary to systemic pressure ratio, by Emmanouilides et al. [20]. The present results are in keeping with the reports of Walsh, and Emmanouilides et al., in which these ventricular depolarization changes have been attributed to the fall of pulmonary arterial pressure, and the replacement of an initial right-to-left shunt, by a left to-right one in the ductus arteriosus, during the first day of life [104, 20].

The values of S-T deviations are of the same magnitude as those found in conventional ECG studies. The present results support the impression that minimal deviations are found in normal newborns, but they can sometimes disappear and reappear. The cause of this cannot be explained according to the present information. The electrocardiographic changes caused by exercise, and anxiety are quite similar to the tachycardic S-T and T wave alterations of the present study and they have been thought to result from alterations in sympathetic tone [82]. The S-T depression shown in Fig. 22, resembles an ischaemic response of the S-T segment [31]. However it is impossible to say if it was caused by alteration of coronary haemodynamics, myocardial metabolics, or vegetative nervous regulation.

The T waves were mainly positive in full-term infants in the present series, and the amplitude even increased during the first hours. Thus, inversion of this deflection did not take place during the observation time, although, in some infants, the amplitude began to decrease. Stern & Lind stated that the inversion was observed in many infants during the first day of life, although it could also occur later [86]. The amplitudes of the premature group were lower and the inversion was also earlier than in the full-term group in the present series. This is in agreement with the reports of Hubaher [38] and Fonseca Costa et al. [22]. The inversion of the right precordial T waves has been attributed to the fall of pulmonary arterial pressure by Dupuis et al. [19], and Emmanouilides et al. [20].

Both positive and and negative T_{V3} waves have been reported on the first day of life, both in full term, and premature infants [17, 20, 22, 54, 107, 112]. After the first day of life the T_{V3} always becomes positive. In the present material, the mean T_{V3} was initially positive for 3 hours, then negative, and finally showed a positive tendency. The infants with negative T waves in the V6 lead were reported, in the article of Emmanouilides et al., to have higher pulmonary arterial pressures than those with positive ones [20].

The T wave amplitudes of the full term, were higher than those of the premature, in the tape recordings of leads V1 and V3. This has been reported in almost every investigation dealing with the ECG of premature infants. The voltages in the present series were of the same magnitude as the corresponding T wave voltages in the investigations mentioned above in this discussion.

The incidence and magnitude of the U wave in the present material were practically equal to those reported in newborn material by Ziegler [112], Michaëlsson [54] and Walsh [107]. The appearance of the U wave was too sporadic for studies of the behaviour of this deflection during the first day of life.

Table XI. Data of the 10 asphyctic premature infants.

No.	Sex	Obstetric history	Birth weight (g)	Apgar score	Duration of tape recording	Serum K (mEq/1)	ECG findings	Response
1	f	normal	820	4	9 h — min	8	sinoatrial block	expired later*
2	m	breech delivery	1100	7	2 h 50 min	—	fixed rate, marked bradycardia, wandering pacemaker nodal and ventricular rhythm	expired during recording*
3	m	normal	1260	8	19 h 22 min	5.7	fixed rate at the beginning, initial I° A V block	expired later*
4	m	breech delivery	1320	1	1 h 11 min	—	fixed rate marked bradycardia, nodal, and ventricular rhythm	expired during recording*
5	f	normal	1450	10	18 h 10 min	4.8	fixed rate, bradycardic rate, marked bradycardia, nodal and ventricular rhythm	expired during recording*
6	m	maternal hypertension transverse lie ablatio placentae, caesarean section	1480	1	19 h 50 min	7.9	fixed rate marked bradycardia, high nodal beats, mid nodal rhythm	recovered
7	m	normal	1810	8	23 h 44 min	8.1	fixed rate tachycardic rate marked bradycardia wandering pacemaker, nodal rhythms, transitional A V block	expired later*
8	f	foetal asphyxia rapid delivery	1800	2	5 h 27 min	—	bradycardic rate marked brady cardia, nodal beats	recovered
9	f	delivery at home	1900	3—7	24 h 5 min	—	fixed rate, marked bradycardia	recovered
10	m	maternal uraemia, caesarean section	2430	5	6 h — min	—	fixed rate marked bradycardia nodal beats	expired after recording*

The autopsy finding in cases No. 1, 2, 3, 4 5 7 and 10 was pulmonary atelectasis with hyaline membranes in cases No. 1 4 and 10. Additionally kernicterus was detected in case No. 3 and intraventricular haemorrhage in case No 7

ASPHYCTIC CASES

Results

In this material there were 10 premature infants, 6 boys and 4 girls, with asphyxia persisting during the ECG recording. The perinatal data and ECG findings of these cases are given in Table XI. The majority had an exceptional delivery small birth weight, and low Apgar score. Three of them died during the ECG recording, and only three recoverd from asphyxia. One of the infants, case No. 8, had a neonatal hypoglycaemia, with a blood sugar of 13 mg per cent. 6 of them had a moderate to grave acidosis at the beginning of the recording. In 2 infants the acid-base balance was normal, and in 2 infants it was not determined. The mean rectal temperature was 34.6 (range 33.2—36.9°) at the beginning of the recording. 3 babies showed a moderate hyperpotassaemia, with serum potassium more than 7 mEq/l

In the asphyctic group, neither means nor ranges of the basal heart rate differed from those of the healthy prematures. The peak heart rates did not exceed those of the healthy prematures. The tendency to occasional tachycardias of more than 170/min, was lower in the asphyctic prematures than in the newborn infants (Tables V VI). The asphyctic prematures showed a frequent predisposition to marked bradycardias of longer duration often associated with apnoeic attacks. No relation of heart rate alterations to other phenomena could be verified. The fixed heart rate pattern was present in 8 of the 10 asphyctic prematures (Fig. 10 Table XI). The fixation of cardiac rate was associated with progressive distress symptoms. No correlation could be demonstrated between the initial rectal temperature and the corresponding basal heart rate.

True arrhytmias were rather common in asphyctic babies (Table VIII, Fig. 12, and Table XI). Only 2 infants (cases 3 and 9) were without any irregularities of cardiac action. Many of the infants had several kinds of arrhytmias following each other Sinoatrial block appeared 6 times, without any syptoms, in the very immature baby No. 1 Wandering pacemaker occurred once in babies No. 2 and 7 in the manner shown in Fig. 14, but in these asphyctic infants, the gradual P wave inversion, and P-R time prolongation were associated with marked bradycardia during an apnoeic spell. Rhythm, originating from the A V nodus, was found in 7 infants. In every case, nodal beats occurred during marked bradycardia. In 5 infants (cases 3, 6, 7 8, and 10), there were sporadic high nodal beats. Long segments of high nodal rhythm occurred in cases 2, 4 and 7 and of mid-nodal rhythm in cases 5 6 and 7 Infant No 5 had, in addition, a short period of low nodal *rhythm*. Usually the nodal rhythm was reversible, but periods of nodal rhythm preceded ventricular rhythm terminally in the very asphyctic babies No. 2, 4 and 5 who died during the tape recording. Examples of arrhythmias in asphyctic infants are presented in Fig. 23. The ECG of the dying heart (case No. 4) is shown in Fig. 28. In all cases, the ventricular rhythm was followed by a complete asystole no ventricular fibrillation was observed.

In the asphyctic group the duration of the P wave ranged from *0.04 to* 0.06 *s that of the P R interval ranged* from 0.09 to 0.14 and the range of the QRS interval was 0.04—0.07 *s*.

Table XI. Data of the 10 asphyctic premature infants.

No.	Sex	Obstetric history	Birth weight (g)	Apgar score	Duration of tape recording	Serum K (mEq/1)	ECG findings	Response
1	f	normal	920	4	9 h — min	8	sinoatrial block	expired later*
2	m	breech delivery	1100	7	2 h 50 min	—	fixed rate marked bradycardia, wandering pacemaker nodal and ventricular rhythm	expired during recording*
3	m	normal	1260	8	19 h 22 min	5.7	fixed rate at the beginning initial I° A V block	expired later*
4	m	breech delivery	1320	1	1 h 11 min	—	fixed rate marked bradycardia, nodal, and ventricular rhythm	expired during recording*
5	f	normal	1450	10	18 h 10 min	4.8	fixed rate, bradycardic rate marked bradycardia, nodal and ventricular rhythm	expired during recording*
6	m	maternal hypertension transverse lie, ablatio placentae caesarean section	1480	1	19 h 50 min	7.9	fixed rate marked bradycardia, high nodal beats, mid nodal rhythm	recovered
7	m	normal	1610	8	23 h 44 min	8.1	fixed rate tachycardic rate, marked bradycardia, wandering pacemaker nodal rhythms, transitional A V block	expired later*
8	f	foetal asphyxia rapid delivery	1800	2	5 h 27 min	—	bradycardic rate, marked brady cardia, nodal beats	recovered
9	f	delivery at home	1900	3—7	24 h 5 min	—	fixed rate marked bradycardia	recovered
10	m	maternal uraemia, caesarean section	2430	5	6 h — min	—	fixed rate marked bradycardia nodal beats	expired after recording*

The autopsy finding in cases No. 1, 2, 3 4 5 7 and 10 was pulmonary atelectasis with hyaline membranes in cases No 1 4 and 10
Additionally kernicterus was detected in case No. 3 and intraventricular haemorrhage in case No. 7

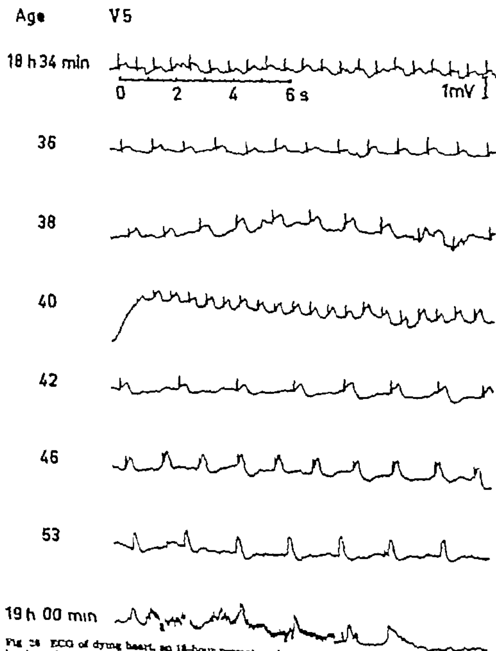


Fig 28 ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV 1 reproduction.

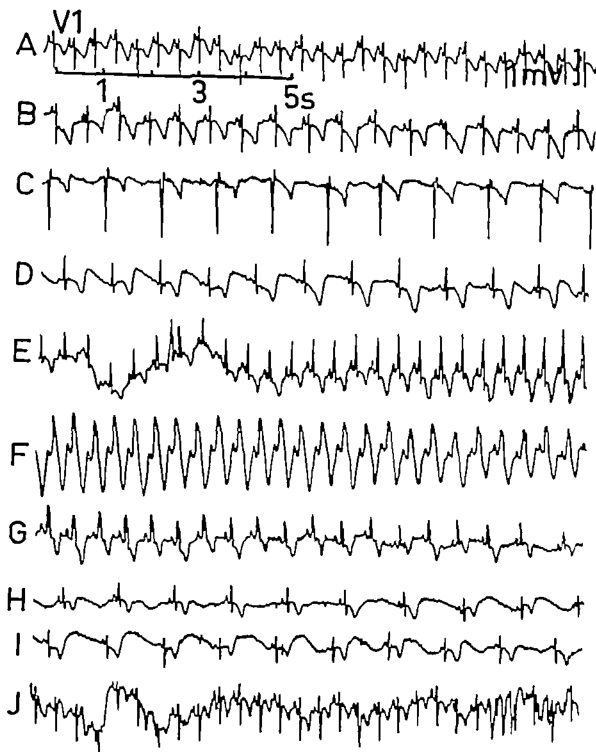


Fig. 25. Successive electrocardiographic abnormalities during asphyctic spell in a 10-hour premature infant (case No. 7) A. normal pattern, B. bradycardia with occasional nodal escape beats, C. marked mid-nodal bradycardia, deformed ventricular depolarization, D reappearance of P wave, occasional nodal escape beats, changed ventricular depolarization, E–G transitional bizarre deformation of ventricular complex, H I. reappearance of brady cardia, occasional nodal escape beats, and J normalization of electric activation. MV 1 reproduction.

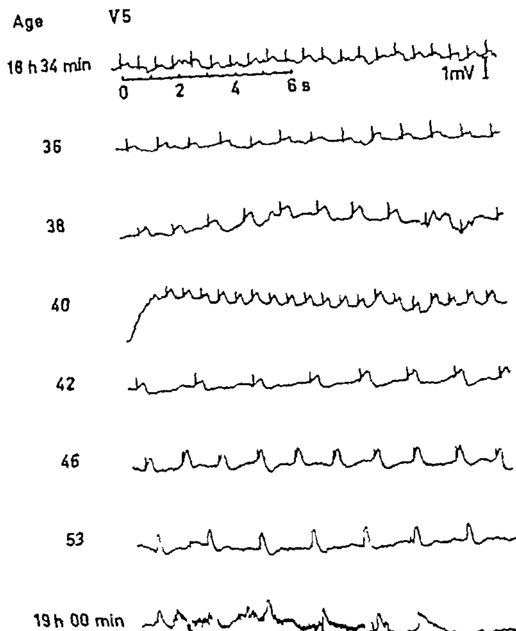


Fig 28 ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV 1 reproduction.

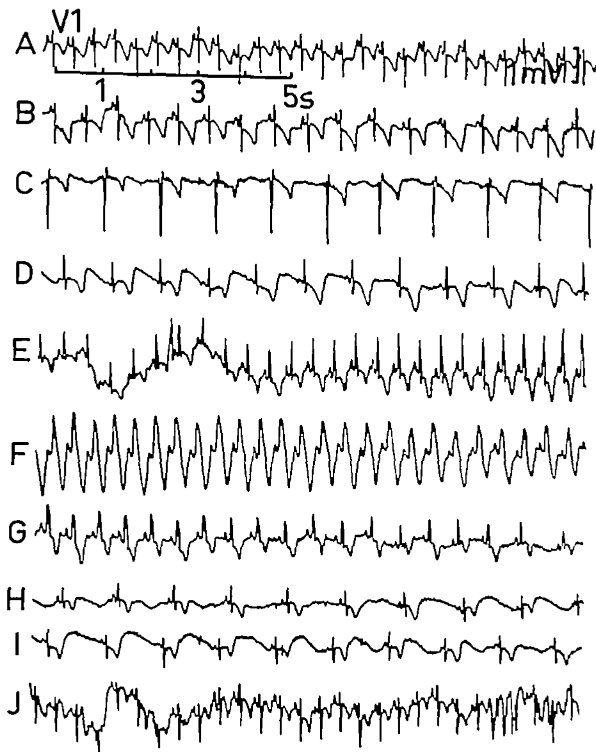


Fig. 25. Successive electrocardiographic abnormalities during asphyctic spell in a 10-hour premature infant (case No. 7) A. normal pattern, B. bradycardia with occasional nodal escape beats, C. marked mid nodal bradycardia, deformed ventricular depolarization, D. reappearance of P wave, occasional nodal escape beats, changed ventricular depolarization, E–G transitional bizarre deformation of ventricular complex, H I. reappearance of brady cardia, occasional nodal escape beats, and J normalization of electric activation. MV 1 reproduction.

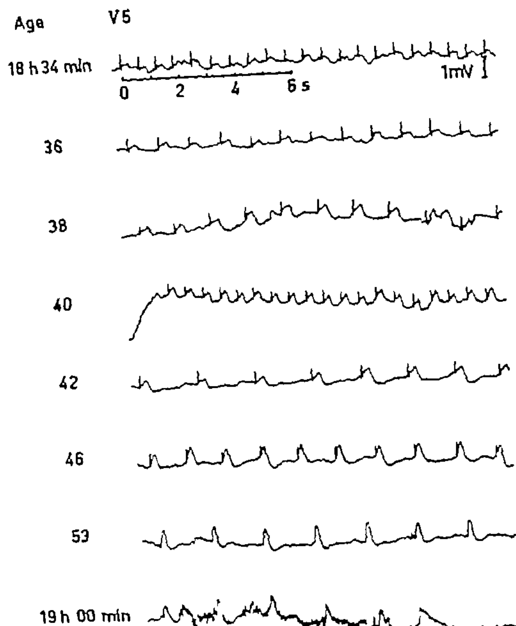


Fig. 28 ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV 1 reproduction.

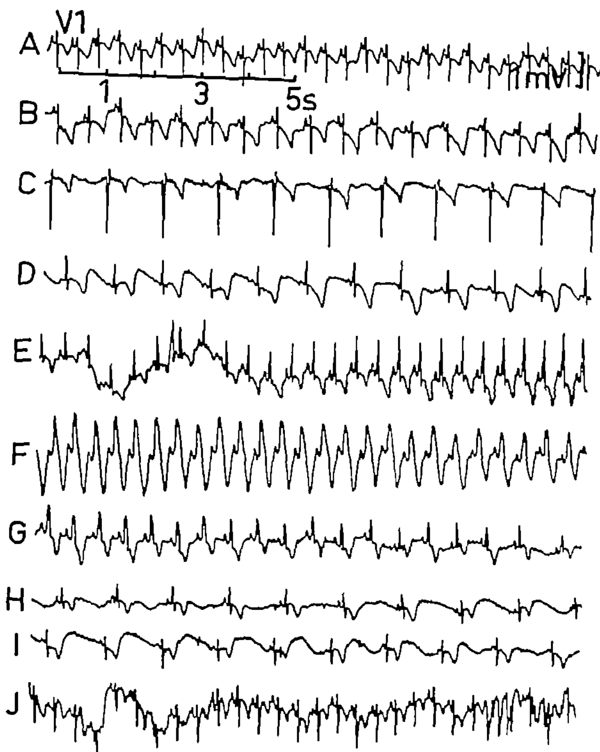


Fig. 25 Successive electrocardiographic abnormalities during asphyctic spell in a 10-hour premature infant (case No. 7) A. normal pattern, B. bradycardia with occasional nodal escape beats, C. marked mid nodal bradycardia, deformed ventricular depolarization, D reappearance of P wave, occasional nodal escape beats, changed ventricular depolarization, E–G transitional bizarre deformation of ventricular complex, H I. reappearance of brady cardia, occasional nodal escape beats, and J normalization of electric activation. MV 1 reproduction.

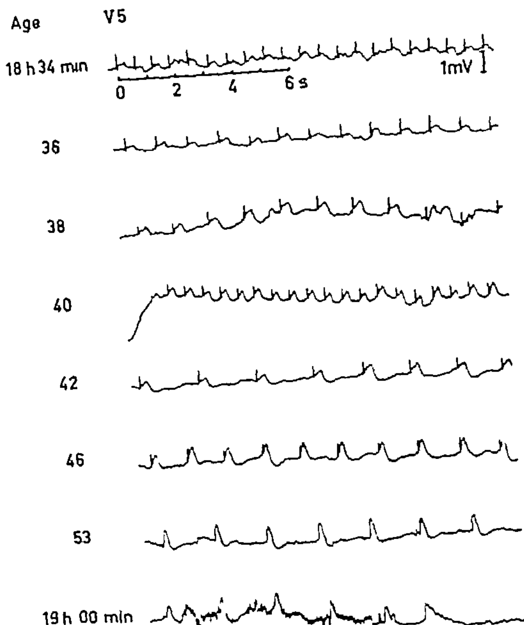


Fig. 28. ECG of dying heart, an 18-hour premature boy (case No. 4). Gradually developing bradycardia with occasional nodal escape beats, continuous nodal rhythm with elevation of S-T segment, ventricular rhythm and finally asystole. MV 1 reproduction.

The durations of the P wave and the P R interval were of the same magni tude, and they behaved in the same manner as the corresponding intervals of the healthy infants, when the nodal and venticular rhythms were excluded. Only one infant, case No 3 had an initial P R interval of 0 14 s, but this decreased during the recording to 0 12 s. A seversible 2 1 A V block appear ed at the age of 24 hours in case No 7 An 0 01 s prolongation of QRS duration developed in cases 5 and 7 in the other asphyctic children the QRS duration decreased as in healthy prematures. The infants with a moderate hyperpotassaemia did not have prolonged P wave P R and QRS interval durations.

All the Q-Tc values of the aspyctic prematures were within the range limits of the healthy prematures, the 2 hour and 24-hour values of which are given in Table IX. The mean values of the asphyctic group were initially the same as those of the healthy premature group The initial QTc values of the asphyctic prematures did not correlate with the rectal tempera tures measured at the beginning of the recording or with the serum potassium concentrations. In 4 infants, cases 1 5 7 and 9 a Q-Tc prolongation of 0 005—0 01 s occurred during the obser vation time, but even these prolonged values were within the corresponding values of healthy prematures. No statistical comparisons were performed between the conduction time values of the asphyctic and healthy premature groups, because of the small number and unhomogenous recording time of the asphyctic group For the same reason, the amplitudes of various deflections have not been compared with the values of healthy prematures. The only clearly distinguishable feature of the amplitudes was a peaked P_{V1} in 6 infants. Grave alterations of the QRS axis were found in the record ings of the very asphyctic babies (Fig. 25 and 26) Left venticular prepon derance was initially present in cases 4, 6, and 7 and it began to develop in cases 1 and 5 The other infants had a typical neonatal right ventricular dominance.

Discussion

Fixation of heart rate, a typical heart rate pattern for asphyctic infants, has been earlier reported by Rudolph et al. [73] and Urbach et al. [93] The disappearance of autonomic nerv ous control of the cardiac pacemaker resulting from depression of medullary centres in progressing asphyxia, has been regarded as an explanation of this phenomenon. The lack of sudden increases of heart rate during fixed rate, has also been observed by Urbach et al. but this pattern was interrupted by marked bradycardias, as in the study of Rudholph et al. and in the present material. Besides these bradycardias, rhythm and condunction disturbances have also been found in asphyctic babies by Ahvenainen & Landtman [1] Usher [94] and Rudolph et al [73] Although abrupt bradycardias are to be detected in full term and healthy premature infants, according to the reports of Morgan et al. [55] Morgan & Guntheroth [57] and Urbach et al. [93] they seem, according to the present results, to be more profuse and of longer duration, in asphyctic infants during the first day of life.

Of the irregularities of cardiac action, extrasystoles and WPW syndrome, have been mentioned by Ahvenainen &

Landtman [1], ventricular rhythm and extrasystoles by Åkerrén [114] and Köttgen & Feyerabend [44] and conduction defects, or wandering pacemaker by Rudolph et al. [73]. Wandering pacemakers, nodal and ventricular rhythms, were found in the present series, but grave irregularities like venticular rhythm appeared only in terminal asphyxia. Delayed atrioventricular conduction, II—III degree A V blocks, prolongation of QRS duration, and bundle branch blocks have been described in asphyctic infants [1 41, 44, 60, 94]. Koivikko described a total A V block appearing during an experimental combined acidosis result ing from asphyxia in a newly born lamb [43]. In the present study there were P R interval and QRS durations, equal to the prolonged ones in the articles mentioned above, but they were within the limits of corresponding values of the normal series. The P R intervals were quite the same in asphyctic and normal newborn, and only slightly prolonged QRS intervals were found by Ringel in the asphyctic group [70]. The conduction times have been reported, by Usher to be prolonged by concentrations of serum potassium over 7,0 mEq/l [94]. Only a transitional A V block was presented in one of th 3 infants with hyperpotassemia of more than this value in the present series. However it must be remembered, that relationships between the intracellular and extracellular potassium contents cause ECG changes, and we have no information about the intracellular levels.

The etiology of these heart rate alterations has not been determined. Most of the cases of Köttgen & Feyerabend had intracranial haemorrhages, and it was thought that the electrocardiographic changes could be of central origin [44]. Also, the material of Ahvenainen & Landtman included 32 patients (25 per cent) with intracranial haemorrhages, but only 4 of them had electrocardiographic changes [1]. In the present asphyctic group, there was only one (case No. 7) who had intraventricular haemorrhage, found at autopsy several days after the recording. Phillips et al. [50] were able to produce marked bradycardias and nodal beats, by vagal stimulation in normal prematures [66]. The present results, and the reports of Walsh (108, 109) on the effect of cord clamping, indicate the role of volume load as an etiological factor in prolonged conduction in healthy newborns. The central blood volume has been reported by Koivikko to increase during asphyxia in newborn lambs [43]. Although the etiology of rhythm and conduction disturbances in general is rather obscure, it would seem evident, that increased vagal tone, or increased sensitivity to vagal tone, may be responsible for these ECG alterations in asphyxia.

Peaked and notched P waves in right precordial chest leads, have been reported in asphyxiated children by Sutin et al. [88, 89] broadening and flattening of the P wave by Usher [94] but according to the article of Keith et al. these do not differ from those of normal newborn infants [41]. The asphyctic babies had higher P waves in the investigation of Ringel, and the amplitude was found to increase in a hypoxia test [70]. Peaked right precordial P waves appeared in the present asphyctic group, but no changes in their form could be demonstrated with the tape recording technique, except those found in association with wandering pacemakers and nodal rhythms. The disappearance of the P

wave mentioned by Usher [94] and Sutin et al. [89] was found in 2 infants (No 6 and 7) and was considered as a mid-nodal rhythm.

Left ventricular preponderance was an electrocardiographic feature of asphyctic newborns in the study of Usher [94] In the investigation of Keith et al. low pulmonary vascular resistance and open ductus arteriosus were associated with this pattern, while asphyctic infants with right ventricular dominance had high pulmonary resistance and open ductus, the prognosis being better in the latter cases [41] The same observation was also made by Sutin et al. [89] Left ventricular dominance began to develop in 2 infants of the present series, both of whom died, and this pattern was initially present in 3 additional cases, 2 of whom also died. According to Keith et al this pattern disappears after the ductus closes. Decreasing QRS amplitudes were observed only in terminal asphyxia in the present study

S-T deviations and pathological flat T waves were the main findings in asphyctic babies in the study of Ahvenainen & Landtman [1] Ringel succeeded in producing the T wave flattening by the hypoxia test in asphyctic newborns [70] Peaked T waves and prolongation of Q-T interval were asphyctic abnormalities in the material of Usher [94] The latter finding was also mentioned by Keith et al., and prolongation of the Q-T interval was also found to develop in the present material. The upright, right precordial T waves remained longer in premature, and asphyctic infants in the same study [41] No uniform alterations of the T wave were observed in the present material. Minimal morphologic changes were detected in the coronary arteries of some asphyctic babies with abnormalities in the ECG by Ahvenainen & Landtman [1] These authors, however together with Ringel [70] Usher [94] and Keith et al. [41] believe that these changes of ventricular repolarization, result from metabolic and electrolyte alterations, caused by asphyxia in the myocardial cells.

CONCLUDING DISCUSSION

When the electrocardiogram of new born infants is studied by means of the long-term recording technique, the main interest will be focused on the areas which are to be reached only by continuous recording, and in which this technique will be expected to be superior to the conventional ECG These areas are heart rate alterations, incidence of arrhythmias, alterations of conduction times, and alterations of the voltages of different deflections of the ECG Because of the alteration nature of this research, the basal pattern of the function must be established for comparison. To get information about the reliability of the method it must be assured that these basal patterns are in agreement with the previous results of the same area. Finally it must be decided how the new features of the neonatal ECG accord with the modern conception of the cardiac physiology of the newborn infant.

According to the present results, the heart rate behaved just as it has been found to behave in the earlier long term electrocardiographic and cardiotachographic studies [15 46, 93, 99 100] The minimal and maximal heart rate values deviate more from the basal level than previously expected. However the minimal phasic variation of the pacemaker activity of the sinoatrial node persists in the maximal heart rates, and this is hard to demonstrate in conventional ECG Fixation of heart rate is a warning sign which may be present in healthy prematures, but is a typical finding in asphyctic infants.

The gradual changes of various electrocardiographic intervals, demonstrated in the present investigation, are in agreement with the results obtained as momentary samples by conventional ECG but the timing of these changes during the first day of life has been determined more exactly in this study As the basal heart rate tends to be minimal at the age of 3—6 hours, the physical activity has also been reported to be minimal during this time [18] It is, however interesting that infants with a birth weight of 2000—3500 g have a lower post-delivery dip of basal heart rate than infants with lower and higher birth weights, and that this difference remained up to 19 hours of age in the present material. During the first 6 hours a clear decrease of conduction times appears, and this shortening continues in the case of the P R interval, up to the age of 14 hours. The present results confirm the observations, and support the hypothesis of Walsh [103] that the same regulating factors will be responsible for these changes of P wave, P R interval, and QRS interval durations. When heart rate alterations, changes in these conduction times, and the effect on them of the moment of clamping of the umbilical cord are all considered, the obvious explanation for these changes may be increase in vagal tone, post partum, as a result of volume load of the heart, but this may also have a direct effect on the ECG, as has been discussed earlier in the articles of Walsh [102, 108 109]. The behaviour of Q-Tc interval is quite different from those of the other intervals. The Q-Tc changes cannot be explained by changes of electrolytes and body temperatures, according to the information obtained in the present study

A contrary result to those of Morgan et al. [55]. Morgan & Guntheroth

wave mentioned by Usher [94] and Sutin et al. [89] was found in 2 infants (No 6 and 7), and was considered as a mid nodal rhythm.

Left ventricular preponderance was an electrocardiographic feature of asphyctic newborns in the study of Usher [94] In the investigation of Keith et al low pulmonary vascular resistance and open ductus arteriosus were associated with this pattern, while asphyctic infants with right ventricular dominance had high pulmonary resistance and open ductus, the prognosis being better in the latter cases [41] The same observation was also made by Sutin et al. [89] Left ventricular dominance began to develop in 2 infants of the present series, both of whom died, and this pattern was initially present in 3 additional cases, 2 of whom also died According to Keith et al this pattern disappears after the ductus closes. Decreasing QRS amplitudes were observed only in terminal asphyxia in the present study

S-T deviations and pathological flat T waves were the main findings in asphyctic babies in the study of Ahvenainen & Landtman [1] Ringel succeeded in producing the T wave flattening by the hypoxia test in asphyctic newborns [70] Peaked T waves and prolongation of Q-T interval were asphyctic abnormalities in the material of Usher [94] The latter finding was also mentioned by Keith et al., and prolongation of the Q-T interval was also found to develop in the present material. The upright, right precordial T waves remained longer in premature and asphyctic infants in the same study [41] No uniform alterations of the T wave were observed in the present material. Minimal morphologic changes were detected in the coronary arteries of some asphyctic babies with abnormalities in the ECG by Ahvenainen & Landtman [1] These authors, however together with Ringel [70] Usher [94] and Keith et al. [41] believe that these changes of ventricular repolarization result from metabolic and electrolyte alterations, caused by asphyxia in the myocardial cells.

SUMMARY

The first section of the present investigation consisted of a description of the ECG tape recording devices of Holter—Avionics, and some additional instruments modified and calibrated for examination of newborn infants. This part also included a comparative study of the signal reproduction in a conventional electrocardiograph, and in different tape recording instruments, the recordings of three chest leads, V1 V3, and V5 having been performed in a material of 30 full-term newborn infants. The results indicated that the time quantities in all the reproductions were equal. No significant differences could be demonstrated between the voltages of the P and T wave reproductions of Electrocardioscanner and those of both writing-out methods and conventional ECG. A marked attenuation of the voltage of the R wave, and particularly that of the S wave, appeared to be produced by the tape recording apparatuses when compared with conventional ECG. This distortion was mainly increased in both writing-out methods. The relationship between the Electrocardioscanner reproduction and the conventional recording of the R and S wave amplitudes in the three chest leads was presented (Fig. 5). An extra upright deflection, post-S spike, was rather frequently found at the end of the QRS complex in the tape recordings, and this deflection was considered to be an artifact caused by the equipment. The ability of the tape recording instruments to repeat S-T deviations proved to be unreliable, but the incidence of these deviations in the material was insufficient for far reaching conclusions. This was also the case with the incidence of the U wave in the material.

In the second section, electrocardiographic changes were studied with long-term recordings in 50 full term, 30 healthy premature, and 10 asphyctic premature newborn infants during the first day of life. The effect of early versus late clamping of the umbilical cord was studied by clamping the cord immediately after delivery in 10 infants of the full-term group. The ECG findings were compared with the information from the obstetric history and clinical observations of the infants, as well as the serum potassium (66 determinations) and calcium (30 determinations) concentrations of the material. The total durations of the recordings were 1248 hours in the full term group, 614 hours in the healthy prematures, and 129 hours in the asphyctic prematures.

The most important findings in the long term recordings were

1) The mean basal heart rate behaved equally in all the three groups, having a minimum level at the age of 3—6 hours (Fig. 8). The infants with a birth

[57] and Church et al [9] is found in the present study in which cardiac arrhythmias appear to be most common in infants with a birth weight of more than 3500 g (up to 4850 g) However the recording times were shorter in the premature group which may have affected the results. In spite of this, it can be stated that both bradycardias and cardiad arrhythmias also appear in full term infants in the first day of life. Both healthy and especially asphyctic infants, seem to be disposed to marked sinus depression evidently of vagal origin, and in these situations a compensatory capture of the pacemaker activity of the lower parts of the heart, mostly of the A V nodus, takes place In the light of the articles of Phillips et al. [66] and Manning & Wallace [51] and the present results, the role of central stimulation and the balance of the autonomic nervous system in the regulation of cardiovascular function, call for further investigation.

The unique electrocardiographic behaviour of the highest birth weight group with a higher heart rate, high incidence of arrhythmias, and shorter Q-Tc interval, is worth noting, but the explanation for this remains open.

The present voltage patterns are peculiar to the recording technique used and can be compared with conventional ECG studies by the aid of the results described in section I of this investigation. However the changes in the amplitudes of various deflections, although the most unreliable of the present results, are in agreement with the previous conventional ECG recordings. Thus, they reflect a decrease in the neonatal right ventricular preponderance even during the first hours, and, in the group of prematures, an additional decrease of the left ventricular forces. These changes have been generally attributed to alterations in pulmonary vascular resistance, and to the closure of the ductus arteriosus.

waves and R/S ratios in the three chest leads indicated diminution of the neonatal right ventricular dominance as early as the first day of life in both healthy groups. There was also a diminution of left ventricular forces in the healthy prematures (Fig. 21). The amplitudes of the R and S waves could be compared with the results of conventional ECG only by means of the diagram in Fig 5

8) The T waves in V1 and V3 leads were generally positive during the observation time in the full term group. The T_{V3} waves were mostly inverted after 3 hours of age in the full-term (Fig. 23). T waves of the healthy prematures were of lower amplitude and they generally became inverted in V3 lead after 6 hours.

The results were compared with earlier ECG studies, and discussed in the light of the present information in neonatal cardiovascular physiology. It could be concluded that valuable data can be obtained by continuous ECG tape recording of the heart action of small infants. The results gave an impression of functional nervous control of the neonatal cardiac action, the maturity of which is possibly related to the maturity of the infant, and this should be considered when the therapy of the disorders of neonatal cardiovascular adaptation is planned.

weight of 2000—3500 g had significantly lower mean basal heart rate levels than the infants weighing less or more (Fig 9) The level of the basal heart rate was mainly 100—125/min, but there was a tachycardic group of 14 per cent of the whole material, with a basal rate al ways more than 125/min, and the ma jority of these cases were prematures. No relationship was found between the basal rate level and sex, number of deliveries of the mother maternal hy pertension, moment of the cord clamping Apgar score, or serum calcium or potassium concentrations. A very low positive correlation could be established between the initial basal heart rate and the rectal temperature of the infant. There was a significant differ ence between the mean basal heart rate levels one hour before and after the first feeding in the full term group

2) The full term infants showed a more prominent and earlier developing tendency to tachycardic phases than the healthy prematures, and the peak heart rate values of the asphyctic prematures never exceeded those of the healthy groups (Fig 8) The maximal cardiac frequency was 260/min, and the max imal duration of a tachycardia with a rate of more than 170/min was 60 min in the whole material. Occasional short enings of P R interval and changes of T wave voltage appeared in connection with the tachycardias.

3) Abrupt bradycardias with a frequency lower than 90/min occurred quite equally in both full term and healthy premature infants, but the asphyctic group expressed a particular tendency to more marked and longer bradycardias than the healthy group (Fig 8)

4) A minimal phasic variation of the heart rate was always present in the full term, and mostly in the premature group even during maximal tachycar dias. Fixation of heart rate was occa sionally seen in the healthy prematures, but this pattern was especially typical for babies with progressive asphyxia.

5) *Cardiac* arrhythmias, mostly asymptomatic, were rather common in all groups (Fig 12 Table VII) Their relative incidence in the healthy infants proved to be highest in the full term weighing more than 3500 g More arrhythmias were found in healthy females than in healthy males. Marked sinus depression, followed by compensatory nodal and ventricular rhythms, was common in asphyctic infants. The cardiac action terminated with ventric ular asystole during the recording of 3 infants.

6) A gradual shortening in the dura tions of the P wave, P R interval, and QRS interval occurred during the first hours of life, this being most pronounced during the first 6—7 hours in the healthy infants (Fig 17) The P R values of the group with the early clamped umbilical cords were signifi cantly lower than those of the late clamped group, during the first 4 hours of life. The behaviour of the Q-Tc interval was different from those of the other conduction times. From the 6th hour of life the Q-Tc values of the healthy prematures were significantly higher than those of the full term, and the group weighing over 3500 g had the lowest Q-Tc values (Fig 19) The 2 hour and 24-hour values of these inter vals are presented in Table IX. A tend ency to prolonged Q-Tc intervals was found in the asphyctic group.

7) No uniform, gradual alterations of P wave voltage were detected. The gradual alterations of the R and S

REFERENCES

1. ARVIDSSON, E. K. and LANDTMAN, B.: Asphyxia neonatorum. Ann. Med. Intern. Fenn. 43 suppl. 18, 1954
2. ALIMURUNG, M. M., LESTER, G. J., NADAS, A. S. and MASSELL, B. F. The unipolar precordial and extremity electrocardiogram in normal infants and children. Circulation 4: 420, 1951
3. ALIMURUNG, M. M. and MASSELL, B. F. The normal P—R interval in infants and children. Circulation 13: 257 1956.
4. ARSTILA, M. HIRVONEN, L., MÄKELÄ, P. PELTONEN, T. and VÄLIMÄKI, I. A continuous electrocardiogram during physical activity and rest. Duodecim (Helsinki) 81 [illegible], 1965
5. BATTRO, A. and MENDY, J. C. Precordial leads in children. Arch intern. Med. 78 31, 1946
6. BAZETT, H. C. An analysis of the time relationship of the electrocardiogram. Heart 7 353, 1920
7. BERLINERBLAU, R. L'électrocardiogramme chez les prématurés. Cardiologia (Basel) 46 184, 1965
8. BURGHARD, E. and WUNDERLICH, A. Das Elektrokardiogramm des Säuglings, des Neugeborenen und des Frühgeborenen. Z. Kinderheilk. 43 [illegible], 1927
9. CHURCH, S. C. MORGAN, B. C. OLIVER, T. K. and GUNTHEROTH, W. C. Cardiac arrhythmias in premature infants. An indication of autonomic immaturity? J. Pediat. 71 542, 1967
10. CLIFTON, R. K. and GRAHAM, F. K. Stability of individual differences in heart rate activity during the newborn period. Psychophysiology 5 37 1968
11. COMMITTEE ON ELECTROCARDIOGRAPHY AMERICAN HEART ASSOCIATION. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation 35 583, 1967
12. CONTIS, G. and LIND, J. Study of systolic blood pressure, heart rate, body temperature of normal newborn infants through first week of life. Acta paediat. (Uppsala) suppl. 146 41, 1963
13. CORDAY, E. BAZICA, V. LANG, T. W. PAPPELBAUM, S., GOLD, M. and BERNSTEIN, H. Detection of phantom arrhythmias and evanescent electrocardiographic abnormalities. J. Amer. med. Ass. 193: 417 1965
14. CRAIGE, E. and HARNED, H. S. Phonocardiographic and electrocardiographic studies in normal newborn infant. Amer. Heart J. 65 180, 1963.
15. DAHL, M. and VÄLIMÄKI, I. The effect of posture on the respiration and heart rate of newborn infants. An impedance pneumographic and electrocardiographic study. To be published
16. DATEY, K. K. and BHARUCHA, P. E. Electrocardiographic changes in the first week of life. Brit. Heart J. 22 175, 1960.
17. DePASQUALE, N. P. and BURCH, G. E. The electrocardiogram, ventricular gradient and spatial vectorcardiogram during the first week of life. Amer. J. Cardiol. 12: 482, 1963.
18. DESMOND, M. M. FRANKLIN, R. R., VALLBONA, C. HILL, R. M. PLUMB, R., ARNOLD, H. and WATTS, J. The clinical behavior of the newly born. I The term baby. J. Pediat. 62 307, 1963
19. DUPUIS, C., DUPUIS, R., ADAMS, F. H. LIND, J. and PELTONEN, T. Further studies on cardiovascular status of normal newborn infants. Effect of adrenaline, acetylcholine, 10 per cent oxygen and 100 per cent oxygen on the electrocardiogram. J. Pediat. 55 649, 1959
20. EMMANOUILIDES, G. C. MOSS, A. J. and ADAMS, F. H. The electrocardiogram in normal newborn infants. Correlation with hemodynamic observations. J. Pediat. 67 578, 1965
21. EMMANOUILIDES G. C. MOSS, A. J. DUFFIE, E. R. Jr. and ADAMS, F. H. Pulmonary arterial pressure changes in human newborn infants from birth to 3 days of age. J. Pediat. 65 327, 1964.
22. FONSECA COSTA, A., PAUL, B. C., LEDBETTER, M. K. and GALMOSH, M. C. The electrocardiogram of the premature infant. Amer. Heart J. 67 4, 1964.
23. FURMAN, R. A. and HALLORAN, W. R. The electrocardiogram in the first two months of life. J. Pediat. 39 307 1951.
24. GÉRARD, R., LAFFY, J. SEICHTER, J. and CROSNIER, J. L'électrocardiogramme du nouveau-né (corrélations électriques et physiologiques). Ann. Pediat. 18 128, 1962.
25. GILSON, J. S. Electrocardiocorder-AVSEP patterns in 37 normal adult men. Amer. J. Cardiol. 16 789, 1965.
26. GILSON, J. S. and GRIFFING, R. E.: Continuous electrocardiograms. Electrodes and lead systems. Amer. J. Cardiol. 8 [illegible], 1961.

ACKNOWLEDGEMENTS

I am deeply grateful to my chief Professor Tuomas Peltonen, M.D., Head of the Children s Hospital, University of Turku, and to Associate Professor Leo Hirvonen, M.D Head of the Cardio-respiratory Research Unit, University of Turku. They aroused my interest in paediatric cardiology and their extensive knowledge of clinical and experi mental cardio-pulmonary neonatology has been of great help to me throughout my studies

My thanks are also due to Professor Kaarlo Hartiala M.D., Head of the Department of Physiology in which the Cardiorespiratory Unit forms a section.

I am very grateful to Professor Fritz Graser M.D., my chief in Städtische Kinderklinik Wiesbaden, West-Germa ny for his invaluable advice and stimu lating interest in my work.

I wish to express my gratitude to Dr Matti Takala M.D Head of the Munici pal Maternity Hospital of Turku, and Dr Eila Maija Harrela, M.D., Head of the Obstetric Department of the District Hospital of Loimaa, and the members of their staffs. I am also grateful to the staff of the neonatal department of the Children s Hospital, without whose continual assistance my work would have been confronted by many practi cal difficulties.

I am indebted to Docent Heikki Frick, M.D Head of the Cardiologic Labora tory Meilahti Clinics, University Central Hospital of Helsinki, for allowing me to use the equipment of this labora tory for comparative analysis of my recordings.

My sincere thanks are due to my very good friends Mr Pekka Mäkelä, M.A., and Mr Timo Åhman, electronic engi neer for their valuable technical assistance.

I wish to thank Mr Matti Grönroos, B.A., Institute of Applied Mathematics, University of Turku, for programming the data processing and checking the statistical aspects of my study I also thank Mrs. Irma Salminen, R.N for her assistance in preparing my results for data processing

Mrs. Aili Ryynänen, M.A., librarian of the Medical Library University of Turku, and her staff helped in the col lection of the literature, for which I am very grateful.

I am very much obliged to Mr Colin Black, B.A., Language Institute of Turku, and Mr Malcolm Cheyne, Uni versity of Dundee, Scotland, for their revision of the manuscript.

I extend my thanks to Mrs. Vuokko Uusitalo and Miss Hellin Aaltonen for their secreterial assistance.

This work was supported by grant of the Finnish Heart Foundation, and grants awarded by the State Commission for Medical Sciences, and Sigrid Jusélius Foundation to the Cardiorespiratory Research Unit.

Turku, September 1969

Ilkka Välimäki

65. PELTONEN, T and HIRVONEN, L. Experimental studies on fetal and neonatal circulation. Acta paediat. scand. suppl. 161, 1965.
66. PHILLIPS, S. J AGATE, F J SILVERMAN, W A. and STEINER, P Autonomic cardiac reactivity in premature infants. Biol. Neonat. (Basel) 6 225, 1964
67 RAIHA, C-E. Das Elektrokardiogramm des Fruhgeborenen. Acta paediat. (Uppsala) 18 448, 1936.
68 RICHMAN, B. and MASTER, A. M. The unipolar chest and extremity lead electrocardiogram in children. Amer Heart J 41 867, 1951.
69 RINGEL, J The electrocardiogram in newborn infants using unipolar thoracic leads. Rev. Czech. Med. 2 242, 1956.
70 RINGEL, J The influence of hypoxia on the electrocardiogram of newborn infants with the asphyxia syndrome Rev Czech. Med. 2 248, 1956
71. ROSKAMM, H., REINDELL, H. BECKHOFF, Ph., BOCHUDER, R KANZO, K. and REINDELL, H. Wirkungsweise und Anwendungsmöglichkeiten des dynamischen elektrokardiographischen Systems von Holter Avionics. Med. Klin 60 785, 1965
72 ROTHFELD, E. K WACHTEL, F W KARLEN, W S and BERNSTEIN A. The evolution of the vectorcardiogram and electrocardiogram of the normal infant I The normal newborn. Amer J Cardiol 8 438, 1961.
73 RUDOLPH, A. J VALLBONA, C and DESMOND, M M Cardiodynamic studies in the newborn III Heart rate patterns in infants with idiopathic respiratory distress syndrome Pediatrics 36 551, 1965
74 SACREZ, R., GEISERT, B. and WILLARD, D A propos de l'électrocardiogramme du prématuré Arch. franç. Pédiat 17 300, 1960.
75 SALMI, T HAMMINEN P and PELTONEN, T The electrocardiogram of premature infants in the first month of life (Bipolar limb leads) Biol Neonat (Basel) 2 148, 1960.
76 SALMI, T HAMMINEN P and PELTONEN, T The electrocardiogram of premature infants in the first month of life (Unipolar chest and limb leads) Biol Neonat (Basel) 3 175, 1961.
77 SANDERS, J S and MARTT J M. Dynamic electrocardiography at high altitude. Arch intern. Med. 118 132, 1966
78 SCHAFFER, A L, BURSTEIN J MASCIA, A V BARENBERG, P L and STILLMAN, N The unipolar electrocardiogram of the newborn infant Amer Heart J 33 122, 1950.
79 SCHAEFER, H and HAAS, H. G Electrocardiography In handbook of physiology Circulation. Vol. 1, ed by W F Hamilton. American Physiological Society Washington, 1962 pp 323—415.
80 SCOTT O and FRANKLIN, D The electrocardiogram in the normal infant. Brit. Heart 25 441, 1963.
81 SHUMAK, K. H. and BROWN, K. W G.: Continuous portable electrocardiography Canad. med. Ass. J 95: 128, 1966.
82. SJOSTRAND, T.. Clinical physiology Svenska bokförlaget, Stockholm, 1967 pp. 573—577
83. SMITH, R. C. Observations on the heart in mothers and the new-born. J Amer med. Ass. 79 3, 1922.
84. SODI-PALLARES, D., PORTILLO, B CISNEROS, F de la CRUZ, M. V and ACOSTA, A R. Electrocardiography in infants and children. Pediat. Clin. N Amer 5 871, 1958.
85. STERN, L. and LIND, J The electrocardiogram at birth. Biol. Neonat. (Basel) 2 34, 1960
86 STERN, L. and LIND, J Neonatal T wave patterns. Acta paediat. (Uppsala) 49 333, 1960
87 STOERMER, J Das unipolar Brustwand-EKG des fruhgeborenen Kindes unter besonderer Berucksichtigung der vektoriellen Verhältnisse Mschr Kinderheilk. 105 414, 1957
88 SUTIN G. J and de V HEESE, H Electrocardiogram in idiopathic respiratory distress syndrome of newborn Lancet 2 532, 1964.
89 SUTIN, G. J HORNER, R de V HEESE, H. and MALAN, A F The electrocardiogram in respiratory distress syndrome. The praecordial P wave as an aid in assessment. Arch. Dis Child 40: 482, 1965.
90 SUTIN, G J and SCHIRE, V The electrocardiogram in the first two days of life. An interracial study Amer Heart J 67 749, 1964
91 THAON, M Contribution à l'étude de l'électrocardiogramme du nouveau-né prématuré. Arch. Mal. Coeur 43 325, 1950.
92 TUDBURY P B and ATKINSON, D. W The electrocardiogram of one hundred normal infants and young children. J Pediat. 36 466, 1950
93 URBACH, J R PHUVICHIT B ZWEIZIG H MILLIGAN, B. CARRINGTON, E. R. LOVELAND, M WILLIAMS, J M LAMBERT R L. DUNCAN, A. M., FARRELL, S. L SIMMONS, P O. and SPURGEON, L L. Instantaneous heart rate patterns in newborn infants. Am J Obstet. Gynec 93 965, 1965.
94 USHER, R. The respiratory distress syndrome of prematurity I Changes in potassium in the serum and the electrocardiogram and effects of therapy Pediatrics 24 562, 1959.
95. VALIMAKI, I Continuous electrocardiorecording during the first day of life in newborn infants Acta physiol scand. 68 suppl. 277 214, 1966.
96. VALIMAKI, I. The use of prolonged electrocardiorecording (Holter Avionics) in detecting cardiac arrhythmias in children. Acta paediat. scand. 56 314, 1967
97 VALIMAKI, I. Cardiac arrhythmias during the first day of life in normal newborn infants. Scand J clin Lab. Invest. 21 suppl. 101 64, 1968.
98 VALIMAKI, I. and MAKELA, P The effect of proximal electrode placement of the central terminal on the electrocardiogram in chest leads in newborn infants. T be published
99. VALLBONA, C., DESMOND, M. M., RUDOLPH, A. J PAP L. F HILL, R. M.,

27 GILSON J S HOLTER, N J and GLASSCOCK, W R. Clinical observations using the Electrocardiocorder AVSEP continuous electrocardiographic system. (Tentative standards and typical patterns) *Amer J Cardiol, 14* 204 1964.

28. GILSON J S., HOLTER, N J and GLASSCOCK, W R. Unusual QRS alterations seen in continuous electrocardiocorder recordings. *Amer Heart J 69* 41, 1965.

29. GRAHAM, F K., CLIFTON R. K. and HATTON H. M. Habituation of heart rate response to repeated auditory stimulation during the first five days of life. *Child Develop 39* 35, 1968.

30. GROS G GORDON A. and MILLER, H. Electrocardiographic patterns of normal children from birth to five years of age. *Pediatrics 8* 349, 1951

31. GUNTHEROTH, W Pediatric lectrocardiography Saunders, Philadelphia and London 1965, pp 126—127

32. HAIT G and GASUL, B. M. The evolution and significance of T wave changes in the normal newborn during the first 7 days of life. *Amer J Cardiol.* 12 494, 1963,

33. HAKULINEN A., HIRVONEN L. and PELTONEN T Response of blood pressure to sucking and tilting in the newborn infant. *Ann. Paediat. Fenn. 8* 54, 1962.

34. HECHT A. F: Der Mechanismus der Herzaktion im Kindesalter seine Physiologie und Pathologie. *Ergebn. ges. Med. Kinderheilk. 11* 324 1913

35 HINKLE L. E., MEYER, J STEVENS, M. and CARVER, S. T Tape recordings of the ECG of active men. Limitations and advantages of the Holter Avionics instruments. Circulation 36 752, 1967

36. HOLTER, N J New method for heart studies. *Science 134* 1214, 1961.

37 HOLZMANN M. Klinische Elektrokardiographie. 4. Auflage. Thieme Stuttgart 1961, pp. 147—151

38. HUBSHER, J A. The electrocardiogram of the premature infant *Amer Heart J 61* 467 1961.

39 JAGIELSKI J NOLIS, J and ROBACZYNSKA, G The electrocardiogram of the newborn. *Kardiol. pol. 7* 87 1964.

40. JAYKKA S. and LAAKSO L. Changes in skin temperature during the first minute of life as signs of circulatory transition t birth. Acta obstet. gynec. scand. 46 359, 1967

41 KEITH, J D., ROSE, V BRAUDO M. and ROWE, R. D The electrocardiogram in the respiratory distress syndrome and related cardiovascular dynamics *J Pediat. 59* 167 1961

42. KESSEL, I. The electrocardiogram on the first day of life. *Brit. Heart J 15* 430, 1953.

43 *KOIVIKKO A.* Cardiovascular responses of the neonatal lamb to hypoxia, hypercapnia and metabolic acidosis. *Acta paed scand.* suppl 191, 1969.

44. KÖTTGEN H. U und FEYERABEND, H. Störungen der Reizbildung und Erregungsleitung im Herzen bei frühgeborenen Kindern *Mschr Kinderheilk 100* 344 1952.

45. LANDTMAN B. Heart arrhythmias in children. *Acta paediat.* (Uppsala) 34 suppl. 1 1947

46. LEVINE, O R., and BLUMENTHAL, S.: Digoxin dosage in premature infants. *Pediatrics* 29 18, 1962.

47 LEVINE, O R. and GRIFFITHS, S. P Electrocardiographic findings in healthy premature infants. *Pediatrics 30* 361, 1962.

48. LIPTON E. L., STEINSCHNEIDER, A. and RICHMOND, J B. Autonomic function in the neonate. VIII Cardio-pulmonary observations. Pediatrics 33 212, 1964.

49. *LONDE, S.* Some aspects of the circulation in the premature infant. *Amer J Dis. Child. 44* 110, 1932.

50. MAKELA, P VALIMAKI, L and AHMAN, T Continuous electrocardiocording by means of Holter' technique. An improved method of paper printing. IV Nordic Meeting on Clinical Physics, Hanko 1968. Proceedings pp. 122—123.

51 MANNING J W and WALLACE, R. W How do cerebral vascular disorders induce ECG changes? Cardiologia *(Basel)* 52 267 1968.

52. MATZDORFF F and SCHMIDT F L. Fortlaufende Ekg Registrierung über mehrere Stunden. *Med. Klin. 61* 573, 1966.

53. MEYER, J L. Some instrument induced errors in the electrocardiogram. *J Amer med. Ass. 201* 351 1967

54. MICHAELSSON M. Electrocardiographic studies in healthy newborn. *Acta paediat. (Uppsala) 48 suppl. 117* 108, 1959.

55. MORGAN B. C., BLOOM, R. S. and GUNTHEROTH, W G. Cardiac arrhythmias in premature infants. Pediatrics 35 658, 1965

56. MORGAN, B. C., DEANE, P G and GUNTHEROTH, W G: Long term continuous electrocardiographic recording in pediatric patients. Pediatrics 38 782, 1966.

57 MORGAN B. C. and GUNTHEROTH, W G Cardiac arrhythmias in normal newborn infants. *J Pediat. 67* 1199, 1965.

58. NADAS, A. Pediatric cardiology 2nd edition Saunders, Philadelphia and London, 1963. pp 64—90.

59. NADRAL A. Die Elektrokardiographie im Säuglingsalter Z. Kinderheilk. 60 283, 1938

60 NADRAL A. Die Elektrokardiographie im Säuglings- und Kindesalter *Erg. ges. Med. Kinderheilk. 60* 668, 1941

61. NICOLAI, G F and FUNARO Das Elektrokardiogram des Säuglings. Zbl. Physiol. 22 58, 1908.

62. NOEGGERATH, C. T Elektrokardiogramme schwächlicher Säuglinge (Frühgeburten, Nahrschäden und Infektionen) Z. Kinderheilk. 8 396, 1913.

63 NORLAND, C. C. and SEMLER, H. J Angina pectoris and arrhythmias documented by cardiac telemetry *J Amer med Ass. 190* 115, 1964.

64 PAINTAL. A. S. A study of right and left atrial receptors. *J Physiol. (Lond.)* 120 596, 1953.

65. PELTONEN, T. and HIRVONEN, L. Experimental studies on fetal and neonatal circulation. Acta paediat. scand. suppl. 161, 1965.
66. PHILLIPS, S. J AGATE, F J SILVERMAN, W A. and STEINER, P.: Autonomic cardiac reactivity in premature infants. Biol. Neonat. (Basel) 6 225, 1964.
67 RÄIHÄ, C-E. Das Elektrokardiogramm des Frühgeborenen. Acta paediat. (Uppsala) 13 440, 1928.
68. RICHMAN, B. and MASTER, A. M The unipolar chest and extremity lead electrocardiogram in children. Amer Heart J 41 887 1951
69. RINSKEL, J The electrocardiogram in newborn infants using unipolar thoracic leads. Rev. Czech. Med. 2 242, 1956.
70 RINSKEL, J The influence of hypoxia on the electrocardiogram of newborn infants with the asphyxia syndrome. Rev Czech. Med. 2 248, 1956
71. ROSKAMM, H., REINDELL, H., BECKHOFF, Ph., BOCHNER, H KONIG, K. and REINDELL, H Wirkungsweise und Anwendungsmöglichkeiten des dynamischen elektrokardiographischen Systems von Holter Avionics. Med. Klin. 60 721, 1965.
72 ROTHFELD, E K., WACHTEL, F W KARLEN, W S and BERNSTEIN, A The evolution of the vectorcardiogram and electrocardiogram of the normal infant. I The normal newborn. Amer J Cardiol 8 438, 1960.
73 RUDOLPH, A J VALLBONA, C. and DESMOND, M. M Cardiodynamic studies in the newborn III Heart rate patterns in infants with idiopathic respiratory distress syndrome Pediatrics 36 551, 1965
74 SACREZ, R GEISERT, R. and WILLARD, D A propos de l'électrocardiogramme du prématuré Arch franc Pédiat. 17 289, 1960.
75 SALMI, T HARKONEN, P and PELTONEN, T The electrocardiograms of premature infants in the first month of life (Bipolar limb leads) Biol. Neonat. (Basel) 3 143, 1961.
76 SALMI, T HARKONEN, P and PELTONEN, T The electrocardiograms of premature infants in the first month of life. (Unipolar chest and limb leads) Biol Neonat (Basel) 3 225, 1961
77 SANDERS, J S and MARTT J M. Dynamic electrocardiography at high altitude. Arch intern. Med. 118 132, 1966.
78 SCHAFFER, A. L, BURSTEIN, J MASCIA, A V BARENBERG, P L. and STILLMAN, N The unipolar electrocardiogram of the newborn infant. Amer Heart J 36 632, 1948.
79 SCHAEFER, H and HAAS, H G Electrocardiography In handbook of physiology: Circulation. Vol 1, ed by W F Hamilton. American Physiological Society Washington, 1962. pp 323—415.
80 SCOTT O and FRANKLIN D The electrocardiogram in the normal infant. Brit. Heart J 25 441, 1963
81 SHUMAN, K. H and BROWN, K. W G. Continuous portable electrocardiography Canad. med. Ass. J 86 138, 1962.
82. SJÖSTRAND, T.. Clinical physiology Svenska bokforlaget, Stockholm, 1967, pp. 373—377
83. SMITH, S. C.: Observations on the heart in mothers and the new-born. J. Amer med. Ass. 79 3, 1922.
84. SODI PALLARES, D PORTILLO, B., CISNEROS, F de la CRUZ, M. V and ACOSTA, A. R.. Electrocardiography in infants and children. Pediat, Clin. N Amer 5 871, 1958.
85. STERN, L. and LIND, J The electrocardiogram at birth. Biol. Neonat. (Basel) 2 34, 1960.
86. STERN, L. and LIND, J Neonatal T-wave patterns. Acta paediat. (Uppsala) 49 329, 1960.
87. STOERMER, J Das unipolar Brustwand-EKG des frühgeborenen Kindes unter besonderer Berücksichtigung der vektoriellen Verhältnisse. Mschr Kinderheilk. 105 414, 1957
88. SUTIN, G. J and de V HEESE, H. Electrocardiogram in idiopathic respiratory distress syndrome of newborn. Lancet 1 622, 1964.
89 SUTIN, G. J HOEKSEL, R de V HEESE, H. and MALAN, A. F The electrocardiogram in respiratory distress syndrome. The precordial P wave as an aid to assessment. Arch. Dis Child 40 402, 1965.
90 SUTIN, G. J and SCHRIRE, V The electrocardiogram in the first two days of life. An interracial study Amer Heart J 67 743, 1964.
91 THAON, M. Contribution à l'étude de l'électrocardiogramme du nouveau-né prématuré. Arch Mal. Coeur 43 826, 1950.
92 TUDBURY P B. and ATKINSON, D. W The electrocardiograms of one hundred normal infants and young children. J Pediat. 38 466, 1950.
93 URBACH, J R PHUVICHIT B., ZWEIZIG, H., MILLIGAN, K., CARRINGTON, E. R., LOVELAND M WILLIAMS, J M., LAMBERT R L., DUNCAN, A. M., FARRELL, S. L., SIMONS, P O. and SPURGEON, L L. Instantaneous heart rate patterns in newborn infants. Am J Obstet. Gynec. 93 965, 1965.
94. USHER, R. The respiratory distress syndrome of prematurity I Changes in potassium in the serum and the electrocardiogram and effects of therapy Pediatrics 24 562, 1959
95. VALIMÄKI, I. Continuous electrocardio-recording during the first day of life in newborn infants. Acta physiol. scand 68 suppl. 277 214, 1966
96 VALIMÄKI, I.: The use of prolonged electrocardiorecording (Holter-Avionics) in detecting cardiac arrhythmias in children. Acta paediat. scand. 56 114, 1967
97 VALIMÄKI, I. Cardiac arrhythmias during the first day of life in normal newborn infants. Scand. J clin. Lab Invest. 21 suppl. 101 64, 1968
98 VALIMÄKI, I. and MÄKELÄ, P The effect of practical electrode placement of the central terminal on the electrocardiogram in chest leads in newborn infants. To be published.
99. VALLBONA, C., DESMOND, M. M., RUDOLPH, A. J PAP L. F HILL, R. M.,

FRANKLIN R. R. and RUSH, J B. Cardiodynamic studies in th newborn. II Regulation of heart rate. *Biol. Neonat. (Basel)* 5 153, 1963.

100 VALLBONA, C., RUDOLPH, A. J and DESMOND M. M.: Cardiodynamic studies in the newborn. IV Heart rate patterns in the non-distressed premature infant. *Pediatrics* 36 560, 1965.

101 VANONI, P R. Rilievi elettrocardiografici nel neonato immaturo. *Minerva pediat.* 10 1041 1958.

102. WALSH, S. Z. P wave duration and P R interval during first week of life. *Brit. Heart J* 25: 42, 1963.

103. WALSH S. Z. Electrocardiographi intervals during first week f life. *Amer Heart J* 66 36, 1963.

104. WALSH, S. Z. The electrocardiogram during the first week of life. *Brit. Heart J* 25 784, 1963.

105. WALSH, S. Z. Evolution of the electrocardiogram of healthy premature infants during the first year of life. *Acta paediat. (Uppsala)* suppl. 145, 1963.

106. WALSH, S. Z. Comparative study of electrocardiograms of healthy premature and full term infants of similar weight. *Amer Heart J* 68 183, 1964.

107 WALSH, S. Z. The S-T segment and T wave during the first week of life. *Brit. Heart J* 26 679, 1964.

108. WALSH, S Z. Early versus late clamping of the cord A comparative study of the ECG in the neonatal period. *Biol. Neonat. (Basel)* 12 343, 1968.

109. WALSH, S. Z. Early clamping versus stripping of cord Comparative study of electrocardiogram in neonatal period. *Brit. Heart J* 31: 122, 1969.

110. WASSERBURGER, R. H. The normal and abnormal unipolar electrocardiogram in infants and children. Williams & Wilkins, Baltimore 1963, pp 6—7

111. WENGER, N K., WATKINS, W L. and HURST J W A preliminary study of the electrocardiogram of th normal premature infant. *Amer Heart J* 62 304, 1961.

112. ZIEGLER, R. F Electrocardiographic studies in normal infants and children. Charles C. Thomas, Springfield, Ill. 1951.

113. AHMAN T and MAKELA, P Improved method of paper printing of ECG recorded on tape by Holter-Avionics system. *Acta physiol. scand.* 68 suppl. 277 228, 1966.

114. AKERREN Y Electrocardiogram in prolonged asphyxia neonatorum. *Acta paediat. (Uppsala)* 38 608, 1949.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge)

134. Müller, Tage, Shunt Operations in Morbus Caeruleus, Results in 161 Cases and Clinical Follow-up. Sw. kr. 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw. kr. 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison bet ·een children with migraine and matched controls. Sw. kr. 25.— 1962
137. Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr. 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children ·ith Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr. 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in th· Treatment of Asphyxia Neonatorum. Sw. kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen, 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wanr-Höckert, Ole and Dowmer, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr. 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr. 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr. .5.— 1963
147. Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl S· immers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Bergen, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr. 20.— 1963
149. Valaes, Titsos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr. 25.— 1963
150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. .5.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study. Sw. kr. 30.— 1964
155. Engström, Ingemar, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr. 25.— 1964
157. Broberger, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type 1 (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm, 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Pohjavuori, T. and Hirvensalo, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. k 1965
164. Böttiger, Margareta, Studies on Immunization ted and Li· Poliovirus Vaccines. Sw. kr. 20.—

165. Glaser, E. M., Cook, C. D., Harris, G. B. C. and Shwachman, H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A M... rial of 570 Danish Cases. Sw. kr. 30.— 1966
168. Troelsborg, W., Focal Spik· Discharges in Children. Longit... nal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right H... in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Öhlberg, Lars, Bacterial Infection in Cases of Perinatal Death... morphological and bacteriological study based on 264 autop... Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chomsky.* Sw. kr. 15.— 1...
173. Walsh, S. Zoe, The Oesophageal Electrocardiogram during ... First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type... clinical study before and after operation ·ith special refere... to haemodynamic function. Sw. kr. 25.— 1967
175. Hiltunen, Pentti, Vectorcardiographic Studies in Newborn ... fants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infecti... Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Berg... 1967. Sw. kr. 35.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatric Practice w... Special Regard to Measurement of the Ventricular Size. ... kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edi... by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody R... sponse to *E. Coli* O-Antigens in Infants and Children w... Urinary Tract Infection, Using ·Passive Haemagglutinatio... Technique. Sw. kr. 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance in t... Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodologic... and Clinical Study. Sw. kr. .5.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Hum... Placental Lipid Metabolism and Transport. Sw. kr. 25.— 19...
184. Robertson, Bengt, The intrapulmonary arterial pattern in norm... infancy and in transposition of the great arteries. Sw. kr. 25... 1968
185. Andersen, Else, Skeletal Maturation of Danish School Childr... in Relation to Height, Sexual Development, and Social Cond... tions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Revie... of the Literature and Report of Nine Cases. Sw. kr. 25.— 19...
187. Karlberg, Petter, *et al.*, The Development of Children in ·Swe... dish Urban Community. A Prospective Longitudinal Study I-V... Sw. kr. 30.— 1968
188. Meeuwisse, Gunnar W. and Melin, Kerstin, Studies in Glucose... Galactose Malabsorption. A Clinical Study of 6 Cases and ·G... netic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbo... Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of th... Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.... 1969
191. Kolvikko, Antti, Cardiovascular Response of the Neonatal Lamb... to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.... 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Disease... in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Peri... natal Mortality. 1969
194. Kaasalainen, Antti, Studies on the Serum Binding of Vitamin B... in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 15.— 1969
196. Roslund, Georg, Social and Psychological Factors Influencing... Hospital Admission of Children. Sw. kr. 20.— 1969
197. Samuls, Raiva, Pseudomonas Infections in ·Paediatric Surgical... Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969

kr 30 —

-ist & W *Boktryckeri AB, Uppsala*

6130/71

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 198 1969

THE COPING PROCESSES IN CHILDHOOD DIABETES

BY MAIJA LIISA KOSKI

[illegible]

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without

134. Möller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr. 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr. 25 — 1962
137 Hansen, A. E. Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw kr 25.— 1962
138. Wallgren, Erik Ivar Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller James A., Jr and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress,* Copenhagen. 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wasz-Höckert, Ole and Donner, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study Sw kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood, An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study Sw. kr. 25.— 1963
144. *Sterky Göran,* Diabetic Schoolchildren. Sw kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw kr. 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P Nylander I., Saltin, B., and Thorén, C., Girl Swimmers, With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply Sw kr 20.— 1963
149. Valaes, Tasos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw kr. 25.— 1963
150. Moe, Peter Johan, Iron Requirements in Infancy Longitudinal studies of iron requirements during the first year of life. Sw kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics,* Lisbon, 1962. Edited by Bo Vahlquist. Sw kr 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children Traumatology Therapy and Prognosis. Sw kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study Sw. kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics. Edited by Bo Vahlquist and Arvid Wallgren.* Sw kr. 25.— 1964
157 Brante, G., Kaijser, K. and Öckerman, P A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm. 1964. Edited by Y Larsson. Sw. kr. 25.— 1965
160. *Öckerman, P A., Glycogen Storage Disease in Sweden.* Sw. kr. 25.— 1965
161. Peltonen, T and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw kr 20.— 1965
162. Landmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C Bronchiectasis: A Review of 187 Cases in Ch up Pulmonary Function Studies in 58. Sw. k
166. Laaksonen, Anna-Liisa, A Prognostic Study o toid Arthritis. Analysis of 544 Cases. Sw kr
167 Iversen, Torben, Leukaemia in Infancy and C rial of 570 Danish Cases. Sw kr. 30.— 1966
168. Trojaborg, W Focal Spike Discharges in C nal Study Sw. kr. 25.— 1966
169 Dahl, Matti, Intracardiac Phonocardiography in Children. Sw. kr 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw.
171. Olding, Lars, Bacterial Infection in Cases of morphological and bacteriological study bas Sw kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chorem*
173. Walsh, S. Zoe, The Esophageal Electrocar *First Week of Life.* Sw. kr 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of clinical study before and after operation to haemodynamic function. Sw. kr. 25.— 19
175. Hiltunen, Pentti, Vectorcardiographic Stud *fants.* Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Sync Sw kr. 20.— 1967
177 *Proceedings of the Fifteenth Northern Paediatr* 1967 Sw. kr. 15.— 1967
178. Sjögren, Irène, Echoencephalography in Pae Special Regard to Measurement of the Ve kr 25.— 1967
179 *Quantitative Studies of the Human Neonatal* by *Göran* Wallgren. Sw kr. 25.— 1967
180. Andersen, Hans Jürgen, Clinical Studies on sponse to *E. Coli* O-Antigens in Infants Urinary Tract Infection, Using Passive Technique. Sw kr. 20.— 1968
181 Koch, Günter Lung Function and Acid-B Newborn Infant. Sw kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone and Clinical Study Sw kr. 25.— 1968
183. Robertson, Alex F., and Sprecher, Howard, Placental Lipid Metabolism and Transport
184. Robertson, Bengt, The intrapulmonary arteri infancy and in transposition of the great 1968
185. Andersen, Ebe, Skeletal Maturation of Dan in Relation to Height, Sexual Development tions. Sw. kr 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi of the Literature and Report of Nine Case
187 Karlberg, Petter, *et al.*, The Development of dish Urban Community A Prospective Long Sw kr. 30.— 1969
188. Meeuwisse, Gunnar W and Melin, Kerstin, Galactose Malabsorption. A Clinical Study netic Study Sw. kr 25.— 1969
189. Fällström, S. P., On the Endogenous Fo Monoxide in Full-Term Newborn Infants. S
190. Hörnblad, P Yngve, Experimental Studies Ductus Arteriosus Utilizing Whole-Body Fr 1969
191. [illegible], Antti, Cardiovascular Response of to Hypoxia, Hypercapnia and Metabolic Ac 1969
192. Vihma, Leena, *Surveillance of Acute Viral R* in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Bi natal Mortality 1969
194. [illegible], Antti, Studies on the Serum Bi in the Newborn Human Infant. Sw. kr. 30.—
195. Thorn, Ingrid, Cerebral Symptoms in the Ne 1969
196. Rosberg, Georg, Social and Psychological *Hospital Admission of Children.* Sw. kr. 20
197 [illegible], Reva, Pseudomonas Infections in a Unit. Sw kr. 20.— 1969
198. Kaila, Maija-Liisa, The Coping Processes in Sw kr 30.— 1969
199 Villankild, Hilda, Tape Recordings of the D Newborn Infants. Sw kr. 30.— 1969

Price Swed. kr 30 —

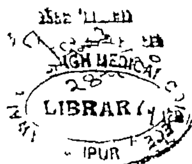
Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 198 1969

THE COPING PROCESSES IN CHILDHOOD DIABETES

BY MAIJA LIISA KOSKI



ALMQVIST & WIKSELL STOCKHOLM SWEDEN

THE COPING PROCESSES IN CHILDHOOD DIABETES

Turku 1969

[illegible]
[illegible]

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 198, 1969

From the Children's Hospital, University of Turku

Turku, Finland

THE COPING PROCESSES IN CHILDHOOD DIABETES

by

Maija-Liisa Koski

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 198, 1969

From the Children Hospital University f Turku
T rku Fi l nd

THE COPING PROCESSES IN CHILDHOOD DIABETES

by

Maija Liisa Koski

CONTENTS

Introduction

The psychological problems of diabetic children have attracted the attention of many well known diabetologists and child psychiatrists. Several articles have touched upon the possible etiological relationship between emotional disturbance and childhood diabetes (18, 143) Other authors have reported that emotional factors in the child's life seem to exercise an influence on the course of the diabetes (64 127) The diabetes itself creates many special problems for the child and his family There is an awareness of being different from other children. Diabetic children experience daily frustrations centered around eating and insulin injections. Authors have been aware that the patient's management of diabetic routines may become an avenue for emotional expression (91 129)

My interest in the study of the psychiatric aspects of childhood diabetes began in 1962, when, as a consultant child psychiatrist for the Children Hospital of the University of Turku, many problems of diabetic children and their parents came up at the meetings with pediatricians and nurses. In spite of the extensive attention given to childhood diabetes in the medical literature, the interplay between the emotional experience of the child and his family and the controllability of the child illness seemed to be in need of further study and discussion.

Introduction

The psychological problems of diabetic children have attracted the attention of many well known diabetologists and child psychiatrists. Several articles have touched upon the possible etiological relationship between emotional disturbance and childhood diabetes (18 143) Other authors have reported that emotional factors in *the child's life seem to exercise an influence on* the course of the diabetes (64 127) The diabetes itself creates many special problems for the child and his family There is an awareness of being different from other children. Diabetic children experience daily frustrations centered around eating and insulin injections. Authors have been aware that the patient' management of diabetic routines may become an avenue for emotional expression (91 129)

My interest in the study of the psychiatric aspects of childhood diabetes began in 1962, when, as consultant child psychiatrist for the Children's Hospital of the University of Turku many problems of diabetic children and their *parents came up at the meetings* with pediatricians and nurses. In spite of the extensive attention given to childhood diabetes in the medical literature, the interplay between the emotional experience of the child and his family and the controllability of the child's illness seemed to be in need of further study and discussion.

The purpose of the present investigation

The aim of the present study is twofold: it tries to find answers to the following questions:

1. How does the family and especially the mother react to the discovery of diabetes in her child? Subsidiary to this: what more lasting reactions and attitudes develop within the family and especially in the mother as time goes on? In the present study these lasting attitudes are called coping processes.

2. How does the child react to the discovery of diabetes in himself? Subsidiary to this, how well adjusted are diabetic children after at least one year' duration of the illness?

In the final part of the study an attempt is made to find possible correlations between various coping processes adopted by both mother and child and the effect of these on diabetic control.

The purpose of the present investigation

The aim of the present study is twofold. It tries to find answers to the following questions:

1. How does the family and especially the mother react to the discovery of diabetes in her child? Subsidiary to this what more lasting reactions and attitudes develop within the family and especially in the mother as time goes on? In the present study these lasting attitudes are called coping processes.

2. How does the child react to the discovery of diabetes in himself? Subsidiary to this, how well adjusted are diabetic children after at least one year's duration of the illness?

In the final part of the study an attempt is made to find possible correlations between various coping processes adopted by both mother and child and the effect of these on diabetic control.

Survey of the literature

Psych som tic r se rch on di betes mellit in dults

Interest in the relationship of *diabetes mellitus* to emotional disturbances dates back to the seventeenth century Thomas Willis described the sweet urine of the diabetic and thought the disease was due to long sorrow" Clinical observations of the relationship between diabetes and mental illness were frequently recorded in the late nineteenth century Savage wrote that "In insanity proper diabetes was rare, but when these two illnesses, which have familiar trends, coincided, the mental illness was of depressive type Maudsley also pointed out that nearly all (diabetic) patients were melancholic (124)

Psychic trauma as a precipitating factor in diabetes

The relationship of diabetes to emotional loss *as first* described by Pike in 1921 in a report of patient who developed diabetes after having lost his wife to another man (108) The role of *emotional depression was further supported* by the observations of Neilson (102)

The opposite view was taken by Menninger in the nineteen-thirties, who *found that* psychic trauma had been an important precipitating factor in only two of his 93 cases of *uncomplicated diabetes (94) Dunbar and* co-workers, in comparative study found preceding emotional traumata in the history of diabetic patients less frequently than in the history of cardiac and fracture patients, and considered that a long period of stress was a more frequent occurrence in the *life* of diabetics *In the diabetic* and cardiovascular groups they found that anxiety was prominent factor (34)

The essential feature, according to Daniels in 1939 was not the trauma, although this may play an important role, but the type of conflict measured in terms of anxiety and tension. Another important factor to bear in mind, according to Daniels, was that repressed emotional tension seems to have greater opportunity *for* discharge through the oluntary nervous system (25) This explains much of the seeming contradiction in the effect of transitory emotional upsets on *sugar metabolism, which so* confused Joslin as to lead him to rule out the whole phenomenon as of little importance (73)

Daniels, in his review of the experimental, general medical, and psychiatric literature of the preceding five years, stated that in general medical writings there were relatively few refe rences to the existence of emotional factors. Further when such references were made there was a tendency to minimize their importance. On the other hand the few papers contributed by clinicians trained in psychological medicine did reveal an awakened interest in, and a new approach to this problem. Observers trained *in psychiatric methods could clearly* demonstrate that neurotic manifestations were frequent in cases of diabetes mellitus (25) Menninger listed nine of a series *of thirty cases studied by him* as psychoneurotic (94)

Daniels stated that any ultimate understanding of the psychopathology associated with diabetes must develop from exhaustive and painstaking study of cases with parallel observations on accompanying physiological changes (25)

Experience gained in World War II produced doubts about the significance of emotional stress as precipitating influence in diabetes (50) Many of the older references relied primarily on *gross observations of very sick patients in a* custodial setting. In addition, the temporal relationship between the metabolic disease and the emotional disturbance was often obscure (124)

Hinkle and Wolf measured changes in blood sugar and blood ketones under stress and concluded that an inappropriate metabolic adaptive mechanism is activated by stressful life situations which represent a loss of affection and security" These authors concluded that the metabolic derangement of diabetes is merely an accentuation of the normal response to carbohydrate starvation triggered by an emotionally threatening life situation (60) More recently Kaplan and Kaplan have reported that *glycosuria is diminished in depressive diabetics* treated with the antidepressant imipramine hydrochloride. When the drug was discontinued *the glycosuria* returned to premedication levels (73)

In the nineteen-fifties Goldner stated that the diabetic patient reacts to severe stress with aggravation of his disease often to the extent of ketoacidosis or coma. Such stressful experiences may be intercurrent diseases or severe trauma as well as sudden and severe emotional disturbances Even the nondiabetic, under such conditions may not infrequently develop similar though less marked metabolic changes characterized by such features as hyperglycemia glycosuria and ketonuria This phenomenon seems to represent part of the nonspecific stress reaction It is exaggerated in the diabetic only because it is here superimposed upon a previously impaired carbohydrate metabolism. The recognition that manifest diabetes mellitus can be aggravated by extrapancreatic functional and environmental factors leads of necessity to questioning whether these factors may also be operative in the causation of the disease From the theoretical point of view one would expect that a disease-aggravating factor when severe enough may become a disease-precipitating or even -causing factor (51)

In the nineteen-sixties Slawson and co-workers evaluated 25 newly diagnosed adult diabetics psychiatrically and obtained the following results 1) fourteen gave a history of definite object loss 2) a further six gave evidence of a loss that could be reasonably inferred 3) ten presented findings of unresolved grief 4) fourteen were considered to be living in an emotionally deprived environment and 5) seven were found to be clinically depressed

They suggested that (adult) diabetic patients may be particularly prone to a specific stress and that their response to emotional deprivation may be a non-adaptive shift to the type of metabolism characteristic of starvation (124)

Danowski discussed emotional stress as a cause of diabetes mellitus as follows "Obviously somewhere between the clearly nondiabetic normal group and the clearly diabetic group there must be a group of people who are developing diabetes mellitus In such individuals a stress which would produce only transient impairment of carbohydrate metabolism in members of the clearly nondiabetic group could theoretically produce permanent diabetes mellitus where none existed previously The crux of the problem is analogous to the question How many straws are needed to break a camel's back? (28)

Characteristic personality structure in diabetes

In the nineteen-thirties several authors m[illegible] attempts to describe a personality struct[illegible] characteristic for diabetes

Menninger described the composite status of a diabetic, which, though suggest[illegible] was on the whole confusing. This may [illegible] accounted for by the fact that ten di[illegible] psychiatric conditions were diagnosed in his ser[illegible] of patients His observations on the effect [illegible] diabetes on intellectual functions are of [illegible] Diminished alertness and awareness of [illegible] environment were reported as characterist[illegible] though the individual was sometimes much mor[illegible] alert to his own condition and events direct[illegible] affecting himself Memory disorders [illegible] mindedness and delayed psychic responses we[illegible] more pronounced in diabetics than in non-diabet[illegible] individuals. (94)

Miles and Root in their psychological stud[illegible] on diabetics found a decrement of 15 per c[illegible] or more in the performance of memory [illegible] attention tasks on testing 39 patients who ha[illegible] hyperglycemia and glycosuria as compared wit[illegible] controls. With treatment they found a rap[illegible] improvement in psychological status approach[illegible] but not quite attaining the normal level. In f[illegible] long-standing treated cases of diabetes they [illegible] that the accuracy and speed of movements [illegible] 20 per cent below normal (98)

Dashiell reported a case in which, in hyp[illegible] and hypoglycemia the patient showed increase[illegible] deficiencies in the same rather than opposit[illegible] directions (29)

The theory that a specific personality typ[illegible] incurs a specific psychosomatic disease [illegible] Dunbar's Dunbar and co-workers described a personality profile of the diabetic patient pointing out that from early childhood an[illegible] before the onset of disease diabetic patients [illegible] difficulties in making the adjustment which [illegible] necessary before one progresses from the infantile state to the more mature independent one consequently such individuals vacillate from [illegible] attitude to the other the impulse [illegible] independence being asserted mainly in words and only very little in action. Paralleling th[illegible] difficulty is an inability to attain mature psychosexual development (34) Dunbar's theory is now only of historical interest because there is considerable evidence to show that it is an oversimplification. However the impact of her

early statements is attested by the frequency with which they are denied. Many later studies of psychosomatic diseases include the statement that "no specific personality type was found" Thus for instance, Bruch stated that although investigations of adult diabetics have made with the object of uncovering characteristic and predisposing traits, so far no uniform picture has emerged (18)

To ic ffe ts of di bet

Menninger reviewing the literature, came to the conclusion that there was a group of toxic cases, to be regarded as diabetic psychoses, but that these represented only small percentage of the number of cases in which diabetes and mental disease were associated. He cited three such cases from his own series. (94)

Rosdrens on searching the literature, found only nine cases, including Menninger three, in which he felt it was justifiable to consider a relationship between diabetes and abnormal psychic states. He concluded that such toxic mental states were independent of personality traits or inherent familial tendencies and attributed them to hyperglycemia. (13) Caution is necessary however before it is concluded that such toxic effects are the primary factors determining the mental picture, as is illustrated in one of the cases reported by Katz (78)

Harris, after a careful study of experimental data showing the ability of the brain to utilize carbohydrate as its main source of energy concluded that in mild or moderately severe diabetes there is little likelihood of any disturbance of brain function, with mental symptoms due to the hyperglycemia alone. In severe diabetes, acetone, keto-acids and betahydroxybutyric acid appear There is disturbance of the electrolyte equilibrium with a loss of bases from the body He concluded that only in severe diabetes will mental symptoms be produced by the toxic effects of the disease and then only in the last stages. He further stated that similarities exist between the mental aberrations seen in psychoses and manifestations in hypoglycemia, whereas such phenomena are seldom seen in hyperglycemia (55)

Attit de and eact on produc d by the d a e

I the liter ture in the nineteen-thirties, depression was found to be one of the most frequent mental symptoms of diabetes mellitus.

Daniels found that depression was an important complication in ten cases of the twenty-three diabetic admissions studied. In five cases the depression was reactive to the loss of a love object prior to the onset of diabetes. Daniels suggested that, when possible a distinction should be drawn between depression of primary nature, which might not be related to the diabetes, and depression secondary to the diabetes. The individual' knowledge that he is suffering from an incurable disease which, on account of the care necessary in treatment, sets him apart from the rest of his fellows in many cases explains his reaction. Much of the hypochondriac self-observation which often accompanies such depressions can be explained in the same way Because it s so natural, however to conclude that such a patient is upset o er his condition, it is possible to miss more fundamental neurotic reactions which may play more primary role. (25)

Beardwood reported two cases of attempted suicide with insulin. One of them was a diabetic woman who had taken 400 units of insulin just prior to admission to hospital. (4)

In the nineteen-forties, Benedek described the traumatic effect of the diagnosis of diabetes mellitus upon the patient, an effect which is believed to be deeper than the anxiety induced by other chronic diseases. The diabetic patient may develop habit of dealing with every external and internal situation in terms of food and of his diabetes. Thus various types of character reaction may be observed in diabetic patients Those whose ego-structure is strong react with extreme compulsiveness in regard to diet while those whose ego-structure is weak respond with overeating and with provocative attitudes in regard to diet. Benedek suggests that the processes secondary to the diabetes may become an integral part of the personality so that we can speak of superstructure of the diabetic individual The individual differences in the adaptation to diabetes probably mainly depend on the integrative capacity of the ego. (9)

Mirsky points out that the onset of diabetes mellitus may produce profound psychologic changes in patients, as well as in various other members of the family Thus their pride may be hurt, their fears and feelings of inadequacy may become intensified, and their aggressive feelings may be aroused, so that they may show great emotional reaction to the onset of the diabetes. (99)

In the nineteen-fifties Goldner stated that the diabetic patient reacts to severe stress with aggravation of his disease often to the extent of ketoacidosis or coma Such stressful experiences may be intercurrent diseases or severe trauma as well as sudden and severe emotional disturbances Even the nondiabetic under such conditions may not infrequently develop similar though less marked metabolic changes characterized by such features as hyperglycemia glycosuria and ketonuria This phenomenon seems to represent part of the nonspecific stress reaction. It is exaggerated in the diabetic only because it is here superimposed upon a previously impaired carbohydrate metabolism The recognition that manifest diabetes mellitus can be aggravated by extrapancreatic functional and environmental factors leads of necessity to questioning whether these factors may also be operative in the causation of the disease From the theoretical point of view one would expect that a disease-aggravating factor when severe enough may become a disease precipitating or even -causing factor (51)

In the nineteen-sixties Slawson and co-workers evaluated 25 newly diagnosed adult diabetics psychiatrically and obtained the following results 1) fourteen gave a history of definite object loss 2) a further six gave evidence of a loss that could be reasonably inferred 3) ten presented findings of unresolved grief 4) fourteen were considered to be living in an emotionally deprived environment and 5) seven were found to be clinically depressed

They suggested that (adult) diabetic patients may be particularly prone to a specific stress and that their response to emotional deprivation may be a non-adaptive shift to the type of metabolism characteristic of starvation (124)

Danowski discussed emotional stress as a cause of diabetes mellitus as follows 'Obviously somewhere between the clearly nondiabetic normal group and the clearly diabetic group there must be a group of people who are developing diabetes mellitus In such individuals a stress which would produce only transient impairment of carbohydrate metabolism in members of the clearly nondiabetic group could theoretically produce permanent diabetes mellitus where none existed previously The crux of the problem is analogous to the question How many straws are needed to break a camel s back? (28)

Characteristic personality structure in diabetes

In the nineteen-thirties several authors ma attempts to describe a personality structu characteristic for diabetes.

Menninger described the composite men status of a diabetic which though suggestiv was on the whole confusing. This may l accounted for by the fact that ten differe psychiatric conditions were diagnosed in his ser of patients His observations on the effect diabetes on intellectual functions are of intere Diminished alertness and awareness of t environment were reported as characteristi though the individual was sometimes much mo alert to his own condition and events direct affecting himself Memory disorders absen mindedness and delayed psychic responses we more pronounced in diabetics than in non-diabet individuals. (94)

Miles and Root in their psychological studi on diabetics, found a decrement of 15 per ce or more in the performance of memory an attention tasks on testing 39 patients who ha hyperglycemia and glycosuria, as compared wit controls. With treatment they found a rap improvement in psychological status, approachin but not quite attaining the normal level. In fiv long-standing treated cases of diabetes they note that the accuracy and speed of movements wa 20 per cent below normal (98)

Dashiell reported a case in which in hyper and hypoglycemia the patient showed increase deficiencies in the same rather than opposit directions (29)

The theory that a specific personality typ incurs a specific psychosomatic disease i Dunbar s Dunbar and co-workers described personality profile of the diabetic patient pointing out that from early childhood and before the onset of disease diabetic patients have difficulties in making the adjustment which is necessary before one progresses from the infantile state to the more mature independent one and consequently such individuals vacillate from one attitude to the other the impulse towards independence being asserted mainly in words and only very little in action." Paralleling this difficulty is an inability to attain mature psychosexual development (34) Dunbar s theory is now only of historical interest because there is considerable evidence to show that it is an oversimplification However the impact of her

early *statements* is attested by the frequency with which they are denied. Many later studies of psychosomatic diseases include the statement that *no specific personality type was found*. Thus, for instance, Bruch stated that although investigations of adult diabetics have made with the *object of uncovering characteristic* and predisposing traits, so far no uniform picture has emerged (18)

Toxic eff cts f di bete

Menninger reviewing the literature, came to *the conclusion that there was a group of toxic* cases, to be regarded as diabetic psychoses, but that these represented only a small percentage of *th, number of cases in which diabetes* and mental disease were associated. He cited three such cases from his own series. (94)

Boudreau, on searching the literature, found only nine cases, including Menninger's three, In which he felt it was justifiable to consider a *relationship between diabetes* and abnormal psychic states. He concluded that such toxic mental states were independent of personality traits or *inherent familial tendencies and attributed them to* hyperglycemia. (13) Caution is necessary however before it is concluded that such toxic *effects are the primary* factors *determining the* mental picture, as is illustrated in one of the cases reported by Katz (78)

Harris, after careful study of experimental data showing the ability of the brain to utilize carbohydrate as its main source of energy *concluded that in mild or moderately severe* diabetes there is little likelihood of any disturbance of brain function with mental symptoms *due to the hyperglycemia* alone. I severe diabetes, acetone, keto-acids and betahydroxybutyric acid appear. There is a disturbance of the electrolyte *equilibrium with loss of bases* from the body. He concluded that only in severe diabetes will mental symptoms be produced by the *toxic effects of the disease and then only in* the last stages. He further stated that similarities exist between the mental aberrations seen in psychoses and manifestations *in hypoglycemia*, whereas such phenomena are seldom seen in hyperglycemia.(55)

Attit de a d eactio s p od ced by the d e e

In the literature in the nineteen *thirties*, depression was found to be one of the most *frequent* mental symptoms of diabetes mellitus.

Daniels found that depression was an important complication in ten cases of the twenty-three diabetic *admissions* studied. In five cases the depression was reactive to the loss of a love object prior to the onset of diabetes. Daniels suggested that, when possible, *distinction* should be drawn between depression of primary nature which might not be related to the diabetes, and depression secondary *to* the diabetes. The individual' knowledge that he is suffering from an incurable disease which on account of the care necessary in treatment, sets *him* apart from *the rest* of his fellows, in many cases explains his reaction. Much of the hypochondriac self-observation which often accompanies such depressions can be explained in the same way. Because it is so natural, however to conclude that such a patient is upset o er his condition, it is possible to miss more fundamental neurotic reactions which may play a more primary role. (25)

Beardwood reported two cases of attempted suicide with insulin. One of them was diabetic woman who had taken 400 units of insulin just prior to admission to hospital. (4)

In the nineteen-forties, Benedek described the traumatic effect of the diagnosis of diabetes *mellitus upon the patient, an effect* which is believed to be deeper than the anxiety induced by other chronic diseases. The diabetic patient *may develop habit of dealing with* every external and internal situation in terms of food and of his diabetes. Thus various types of character *reaction may be observed in diabetic* patient. Those whose ego-structure is strong react with extreme compulsiveness in regard to diet while *those whose ego-structure is* weak respond with overeating and with provocative ttitudes in regard to diet. Benedek suggests *that the processes secondary to the diabetes* may become an integral part of the personality so that we can speak of superstructure of *the diabetic individual*. The individual differences in the adaptation to diabetes probably mainly depend on the integrative capacity of the ego. (9)

Mirsky points out that the onset of diabetes mellitus may produce *profound psychologic* changes in patients, as well as in various other members *of* the family. Thus their pride may be hurt, their fears and feelings *of inadequacy* may become intensified, and their aggressive feelings may be aroused, so that they may show great emotional reaction to the onset *of the diabetes*. (99)

In the nineteen-fifties Goldner stated that the diabetic patient reacts to severe stress with aggravation of his disease often to the extent of ketoacidosis or coma. Such stressful experiences may be intercurrent diseases or severe trauma as well as sudden and severe emotional disturbances Even the nondiabetic under such conditions may not infrequently develop similar though less marked metabolic changes characterized by such features as hyperglycemia glycosuria and ketonuria This phenomenon seems to represent part of the nonspecific stress reaction. It is exaggerated in the diabetic only because it is here superimposed upon a previously impaired carbohydrate metabolism The recognition that manifest diabetes mellitus can be aggravated by extrapancreatic functional and environmental factors leads of necessity to questioning whether these factors may also be operative in the causation of the disease From the theoretical point of view one would expect that a disease aggravating factor when severe enough may become a disease precipitating or even -causing factor (51)

In the nineteen-sixties Slawson and co-workers evaluated 25 newly diagnosed adult diabetics psychiatrically and obtained the following results 1) fourteen gave a history of definite object loss 2) a further six gave evidence of a loss that could be reasonably inferred, 3) ten presented findings of unresolved grief 4) fourteen were considered to be living in an emotionally deprived environment and 5) seven were found to be clinically depressed

They suggested that (adult) diabetic patients may be particularly prone to a specific stress and that their response to emotional deprivation may be a non-adaptive shift to the type of metabolism characteristic of starvation. (124)

Danowski discussed emotional stress as a cause of diabetes mellitus as follows "Obviously somewhere between the clearly nondiabetic normal group and the clearly diabetic group there must be a group of people who are developing diabetes mellitus In such individuals a stress which would produce only transient impairment of carbohydrate metabolism in members of the clearly nondiabetic group could theoretically produce permanent diabetes mellitus where none existed previously The crux of the problem is analogous to the question How many straws are needed to break a camel s back? (28)

Characteristic personality structure in diabetes

In the nineteen-thirties several authors made attempts to describe a personality structure characteristic for diabetes.

Menninger described the composite mental status of a diabetic which though suggestive, was on the whole confusing This may be accounted for by the fact that ten different psychiatric conditions were diagnosed in his series of patients. His observations on the effect of diabetes on intellectual functions are of interest. Diminished alertness and awareness of the environment were reported as characteristic though the individual was sometimes much more alert to his own condition and events directly affecting himself Memory disorders, absent mindedness and delayed psychic responses were more pronounced in diabetics than in non-diabetic individuals (94)

Miles and Root in their psychological studies on diabetics found a decrement of 15 per cent or more in the performance of memory and attention tasks on testing 39 patients who had hyperglycemia and glycosuria as compared with controls With treatment they found a rapid improvement in psychological status approaching but not quite attaining the normal level In five long-standing treated cases of diabetes they noted that the accuracy and speed of movements was 20 per cent below normal (98)

Dashiell reported a case in which in hyper and hypoglycemia the patient showed increased deficiencies in the same rather than opposite directions (29)

The theory that a specific personality type incurs a specific psychosomatic disease is Dunbar s Dunbar and co-workers described a personality profile of the diabetic patient pointing out that from early childhood and before the onset of disease diabetic patients have difficulties in making the adjustment which is necessary before one progresses from the infantile state to the more mature independent one and consequently such individuals vacillate from one attitude to the other the impulse towards independence being asserted mainly in words, and only very little in action " Paralleling this difficulty is an inability to attain mature psychosexual development (34) Dunbar s theory is now only of historical interest, because there is considerable evidence to show that it is an oversimplification However the impact of her

Psychos matic search on diabetes mellitus in children

According to Kessler more, perhaps, has been written about diabetes from the psychological standpoint than about any other childhood disease, excluding those considered psychosomatic. The major concerns have been, 1) the relationship between the emotions and the medical course of the diabetes and 2) emotional reactions to the management of the illness. (80)

Dietary restrictions and the daily injections of insulin are liable to cause many problems. The mother relationship with her child is strained by prohibitions of certain foods and infliction of pain at the injection. Children are apt to attribute the illness to eating too many sweets and so may feel guilty. Similarly if the sugar metabolism gets out of control, both the parents and the child may feel guilty.

In two of the cases studied by Daniels, diabetes occurred in childhood at time when an infantile neurosis appeared to be acute. The factor precipitating the neurosis may also conceivably have precipitated the diabetes. That there actuall was a link between the neurosis and the onset of diabetes certainly could not be proved (24)

Fischer and Dolger described dullness immaturity and dependency as characteristics of oung diabetic patients (44). Benedek suggested that no chronic disease of childhood produces more anxiety in the mother than diabetes mellitus (9). On the other hand, in Korsch view virtually all parents of physically handicapped children have feeling of guilt and of personal responsibility for the handicap (82)

Bruch stated that the need for adequate metabolic treatment of the diabetic condition so as to insure more normal growth and freedom from physical ill-health had long stood in the foreground of medical thinking, but it was only in the nineteen-thirties that the psychologic problems of diabetic children had gained attention. Her own observations were made on 37 diabetic children. As was the fashion in psychosomatic medicine at that time she was concerned with specific personality structure in diabetic children and psychological characteristics of the family setting in which diabetes had developed. One focus of Bruch inquiry was upon factors which may hav been of traumatic significance in the development of diabetes. There were disturbances in family relationships, such as divorce, *birth of* a sibling, death, boarding out with relatives, etc., in 10 of the 37 cases. Only in one case had the family connected this event with the onset of diabetes while in another case a relationship was later suspected between the onset of diabetes and the child's separation from the father who had played an affectionate role in the life of his son.

As Bruch remarked, if the disease had existed for several years it is difficult if not impossible, to differentiate between the pre-existing psychologic picture and the influence f the diabetic regimen on the family. She differentiated three main ways in which the mothers reacted towards the diabetic regimen

1 ***A tolerant and relaxed acceptance*** of the responsibility. This attitude seemed to produce fairly satisfactory regulation and adjustment in the children. While it may be recognized as the most desirable attitude, it was the least frequent in Bruch cases.

2 *A perfectionistic overcontrol* With this attitude, all tasks become expressions of the mother absolute need to do the right thing. Here the basic attitude toward the child is aggressive and subduing. Yet this overcontrol of the child was characteristically associated with satisfactory regulation of the diabetes, and these families were rated as good and co-operative. Frequently behavior difficulties occurred in other fields, such as stealing, poor school-work or sudden rebelliousness.

3 *Erratic or persistently poor co-operation* regarding the medical regimen. Such an attitude, of course produced poor control, with marked fluctuation in the degree of regulation. Satisfactory regulation was always the exception. Despite these consequences, this attitude was the most frequent. (18)

Since the nineteen-forties many authors have stressed the psychological problems of young diabetics.

Mason called attention to the existence of diabetes as the background illness for suicidal behavior in three disturbed adolescent girls (92)

Katz mentioned the greater incidence of behavior problems in diabetic than in nondiabetic children (77)

Stearns pointed out that many young diabetics exhibit gamut of unreasonable behavior which can be interpreted as essentially self-destructive. Such behavior was most frequently exhibited when major life adjustments had to be made

In the nineteen-fifties Smith and Brown attempted to evaluate the responses of twenty five adult diabetics to their illness. The group was found to present two different types of responses a group of 19 with obesity and minimal concern over their condition and a group of 6 patients with marked concern about their long standing neurotic symptoms It was felt that the lack of concern observed in the 19 obese diabetics was an important factor in their not keeping to the dietary regimen (125)

Beaser points out that the diabetic's basic difficulty adhering to his diet is psychological rather than physiological Also he adds even superficial psychiatric observation of diabetic patients reveals that many kinds of environmental and intra psychic factors are important in influencing the diabetes through food intake. (5)

Tunbridge states that the reasons why patients fail to maintain satisfactory control fall into three main categories psychological social and educational and that the psychological causes are especially prominent in the juvenile diabetic. He reiterates the belief that the trauma caused by the discovery of diabetes is deeper and more disturbing than the anxiety caused by other chronic diseases. (144)

Palmer emphasized the uniqueness of diabetes mellitus among chronic and incurable diseases. He stated that the diabetic is faced with interminable diet restriction which virtually eliminates many highly gratifying foods There is no other disease which requires daily self administration of medication with a hypodermic syringe with the threat of disaster if this ritual is not observed The nearness of disaster is further emphasized by the institution of daily urine testing in which the patient is confronted with evidence of any defection from strict control The success and failure of diabetic control is largely dependent upon the active participation of the patient in the treatment Obviously far more responsibility for the control of his disease is placed on the patient than in many other diseases (105)

Psychotherapy in diabetes

Authorities agree that more adequate treatment of diabetics requires an understanding of the patient as a person and not merely as a case of disturbed sugar metabolism

Bauch in the nineteen-thirties, appears to have been the first to attempt to develop systematic psychotherapy for diabetics as a supplement to general medical care. He pointed out that sugar excretion is frequently the reaction of the patient to external and internal stimuli particularly those of an emotional nature, and that tension and irritability are common in the diabetic. He reports the systematic use of relaxation therapy (3) Jacobson calls attention to the fact that diabetic patients often display an extraordinary degree of restlessness and anxiety and states that relaxation therapy is indicated (71)

Herskowitz pointed out the importance of re education and encouragement and maintained that classes instituted for instruction in matters of diet and regimen are among the greatest aids in helping the mental hygiene of the diabetic patient (58) The refractory patient who disregards rules often calls for careful psychiatric study as the usual disciplinary approach may tend to aggravate the situation unless social and personality factors have been carefully evaluated (24)

In the nineteen fifties Stearns stated that in most instances lack of success in diabetic control can be ascribed to inadequate co-operation of the patients, who do not follow the prescribed regimen satisfactorily The precipitating factor however may be some action or attitude of the physician based on his lack of awareness of the real significance of the patient's behavior or lack of skill in handling the issues arising in the course of treatment. The author indicated that the diagnosis of diabetes means different things to different patients and that only a few approach the problem realistically He suggested that it would be more effective to limit initial reassurance to emphasizing the positive aspects of the situation and to answering the questions asked by the patient in the least disturbing manner The specific anxieties could be dealt with subsequently The problem areas center around the necessity to follow a restricted diet and the necessity of insulin injections. (128)

Beaser reported that insulin therapy of diabetes may be complicated by emotional tensions These may engender a variety of symptoms which tend to complicate the ambulatory treatment (5)

Dobson with his co-workers described a clinic set up for the better handling of the social economic and medical factors so important in the care of diabetic patients. This included the services of a social worker (33)

P y hosomatic research on diabetes mellitus in child en

According to Kessler more, perhaps, has been written about diabetes from the psychological standpoint than about any other childhood disease, excluding those considered psychosomatic. The major concerns have been. 1) the relationship between the emotions and the medical course of the diabetes and 2) emotional reactions to the management of the illness. (80)

Dietary restrictions and the daily injections of insulin are liable to cause many problems. The mother relationship with her child is strained by prohibitions of certain foods and infliction of pain at the injection Children are apt to attribute the illness to eating too many sweets and so may feel guilty Similarly if the sugar metabolism gets out of control, both the parents and the child may feel guilty

In two of the cases studied by Daniels diabetes occurred in childhood at a time when an infantile neurosis appeared to be acute. The factor precipitating the neurosis may also conceivably have precipitated the diabetes. That there actually was a link between the neurosis and the onset of diabetes certainly could not be proved. (24)

Fischer and Dolger described dullness, immaturity and dependency as characteristics of young diabetic patients (44) Benedek suggested that no chronic disease of childhood produces more anxiety in the mother than diabetes mellitus (9) On the other hand, in Korsch view virtually all parents of physically handicapped children have feeling of guilt and of personal responsibility for the handicap (82)

Bruch tated that the need for adequate metabolic treatment of the diabetic condition so as to insure more normal growth and freedom from physical ill-health had long stood in the foreground of medical thinking, but it was only in the nineteen thirties that the psychologic problems of diabetic children had gained attention. Her own observations were made on 37 diabetic children As was the fashion in psychosomatic medicine at that time she was concerned with a specific personality structure in diabetic children and psychological characteristics of the family setting in which diabetes had developed. One focus of Bruch inquiry was upon factors which may have been of traumatic significance in the development of diabetes There were disturbances in family relationships, such as divorce, birth of a sibling, death boarding out with relatives etc., in 10 of the 37 cases. Only in one case had the family connected this event with the onset of diabetes, while in another case a relationship was later suspected between the onset of diabetes and the child's separation from the father who had played an affectionate role in the life of his son.

As Bruch remarked, if the disease had existed for several years it is difficult, if not impossible, to differentiate between the pre-existing psychologic picture and the influence of the diabetic regimen on the family She differentiated three main ways in which the mothers reacted towards the diabetic regimen.

1 *A tolerant and relaxed acceptance* of the responsibility This attitude seemed to produce fairly satisfactory regulation and adjustment in the children. While it may be recognized as the most desirable attitude, it was the least frequent in Bruch's cases

2 *A perfectionistic overcontrol* With this attitude, all tasks become expressions of the mother's absolut need to do the right thing Here the basic attitude toward the child is aggressive and subduing. Yet this overcontrol of the child was characteristically associated with satisfactory regulation of the diabetes and these families were rated as good and co-operative Frequently behavior difficulties occurred in other fields, such as stealing, poor school-work or sudden rebelliousness

3 *Erratic or persistently poor co-operation* regarding the medical regimen Such an attitude, of course, produced poor control, with marked fluctuation in the degree of regulation. Satisfactory regulation was always the exception. Despite these consequences, this attitude was the most frequent (18)

Since the nineteen-forties, many authors have stressed the psychological problems of young diabetics.

Mason called attention to the existence of diabetes as the background illness for suicidal behavior in three disturbed adolescent girls (92)

Katz mentioned the greater incidence of behavior problems in diabetic than in nondiabetic children (77)

Stearns pointed out that many young diabetics exhibit gamut of unreasonable behavior which can be interpreted as essentially self-destructive. Such behavior was most frequently exhibited when major life adjustments had to be made

In the nineteen-fifties Smith and Brown attempted to evaluate the responses of twenty-five adult diabetics to their illness. The group was found to present two different types of responses a group of 19 with obesity and minimal concern over their condition and a group of 6 patients with marked concern about their long-standing neurotic symptoms It was felt that the lack of concern observed in the 19 obese diabetics was an important factor in their not keeping to the dietary regimen. (125)

Beaser points out that the diabetic s basic difficulty adhering to his diet is psychological rather than physiological Also he adds even superficial psychiatric observation of diabetic patients reveals that many kinds of environmental and intra-psychic factors are important in influencing the diabetes through food intake. (5)

Tunbridge states that the reasons why patients fail to maintain satisfactory control fall into three main categories psychological social and educational and that the psychological causes are especially prominent in the juvenile diabetic. He reiterates the belief that the trauma caused by the discovery of diabetes is deeper and more disturbing than the anxiety caused by other chronic diseases. (144)

Palmer emphasized the uniqueness of diabetes mellitus among chronic and incurable diseases He stated that the diabetic is faced with interminable diet restriction which virtually eliminates many highly gratifying foods. There is no other disease which requires daily self administration of medication with a hypodermic syringe with the threat of disaster "if this ritual is not observed The nearness of disaster is further emphasized by the institution of daily urine testing, in which the patient is confronted with evidence of any defection from strict control The success and failure of diabetic control is largely dependent upon the active participation of the patient in the treatment Obviously far more responsibility for the control of his disease is placed on the patient than in many other diseases (105)

Psychotherapy in diabetes

Authorities agree that more adequate treatment of diabetics requires an understanding of the patient as a person and not merely as a case of disturbed sugar metabolism

Bauch, in the nineteen-thirties appears to have been the first to attempt to develop systematic psychotherapy for diabetics as a supplement to general medical care He pointed out that sugar excretion is frequently the reaction of the patient to external and internal stimuli particularly those of an emotional nature, and that tension and irritability are common in the diabetic. He reports the systematic use of relaxation therapy (3) Jacobson calls attention to the fact that diabetic patients often display an extraordinary degree of restlessness and anxiety and states that relaxation therapy is indicated (71)

Herskowitz pointed out the importance of re-education and encouragement, and maintained that classes instituted for instruction in matters of diet and regimen are among the greatest aids in helping the mental hygiene of the diabetic patient (58) The refractory patient who disregards rules often calls for careful psychiatric study as the usual disciplinary approach may tend to aggravate the situation unless social and personality factors have been carefully evaluated (24)

In the nineteen-fifties Stearns stated that in most instances lack of success in diabetic control can be ascribed to inadequate co-operation of the patients who do not follow the prescribed regimen satisfactorily The precipitating factor however may be some action or attitude of the physician based on his lack of awareness of the real significance of the patient s behavior or lack of skill in handling the issues arising in the course of treatment The author indicated that the diagnosis of diabetes means different things to different patients, and that only a few approach the problem realistically He suggested that it would be more effective to limit initial reassurance to emphasizing the positive aspects of the situation and to answering the questions asked by the patient in the least disturbing manner The specific anxieties could be dealt with subsequently The problem areas center around the necessity to follow a restricted diet and the necessity of insulin injections (128)

Beaser reported that insulin therapy of diabetes may be complicated by emotional tensions These may engender a variety of symptoms which tend to complicate the ambulatory treatment (5)

Dobson with his co-workers described a clinic set up for the better handling of the social economic and medical factors so important in the care of diabetic patients This included the services of a social worker (33)

Psy h som tic research on di betes mellit s in children

According to Kessler more, perhaps, has been written about diabetes from the psychological standpoint than about any other childhood disease, excluding those considered psychosomatic. The major concerns ha e been, 1) the relationship between the emotions and the medical course of the diabetes and 2) emotional reactions to the management of the illness. (80)

Dietary restrictions and the daily injections of insulin are liable to cause many problems. The *mother's relationship with her child is strained* by prohibitions of certain foods and infliction of pain at the injection. Children are apt to attribute the illness to eating too many sweets and so may feel guilty. Similarly if the sugar *metabolism gets out of control*, both the parents and the child may feel guilty.

In two of the cases studied by Daniels, diabetes occurred in childhood at time when an *infantile neurosis appeared* to be acute. The factor precipitating the neurosis may also conceivably have precipitated the diabetes. That there actuall was a link between the neurosis and the onset of diabetes certainly could not be proved. (24)

Fischer and Dolger described dullness, immaturity and dependency as characteristics of young diabetic patients. (44) Benedek suggested that no chronic disease of childhood produces *more anxiety in the mother than diabetes* mellitus. (9) On the other hand in Korsch's *view virtually* all parents of physically handicapped children have feeling of guilt and of personal responsibility for the handicap. (82)

Bruch stated *that the need for adequate* metabolic treatment of the diabetic condition so as to insure more normal growth and freedom from physical ill-health had long stood in the foreground of medical thinking, *but it was only* in the nineteen-thirties that the psychologic problems of diabetic children had gained attention. *Her* own observations were made on 37 diabetic children. As was *the fashion in* psychosomatic medicine at that time, she was concerned with a specific personality structure in diabetic children and psychological characteristics of the family setting in which diabetes had developed. One focus of Bruch's inquiry was upon factors which may have been of traumatic significance in the development of diabetes. There were disturbances in family relationships, such as divorce, birth of a sibling, death, *boarding out with relatives* etc., in 10 of the 37 cases. Only in one case had the family connected this event with the onset of diabetes, while in another case a relationship was later suspected between the onset of diabetes and *the child's separation from the father* who had played an affectionate role in the life of his son.

As Bruch remarked, if the disease had existed for several years t is *difficult, if not impossible, to differentiate* between the pre-existing psychologic picture and the influence of the diabetic regimen on the family. She differentiated three main ways in which the mothers reacted towards the diabetic regimen.

1 *A tolerant and relaxed acceptance* of the responsibility. This ttitude seemed to produce fairly satisfactory regulation and adjustment in the children. While it may be recognized as the most desirable ttitude, *it was the least frequent* in Bruch's cases.

2 *A perfectionistic overcontrol*. With this attitude, all tasks become expressions of the mother's absolute need to do the right thing. Here the *basic attitude toward the child is aggressive and* subduing. Yet this overcontrol of the child was characteristically associated with satisfactory regulation of the diabetes, and these families were rated as good and co-operative. Frequently behavior difficulties occurred in other fields, such as stealing, poor school-work or sudden rebelliousness.

3 *Erratic or persistently poor co-operation regarding the medical regimen. Such an attitude* of course produced poor control, with marked fluctuation in the degree of regulation. Satisfactory regulation was always the exception. Despite *these consequences, this attitude was the* most frequent. (18)

Since the nineteen-forties, many authors have *stressed* the psychological problems of young diabetics.

Mason called attention to the existence of diabetes as the background illness for suicidal behavior in three disturbed adolescent girls. (92)

Katz mentioned the greater incidence of behavior problems in diabetic than in nondiabetic children. (77)

Stearns pointed out that many young diabetics *exhibit a gamut* of unreasonable behavior which can be interpreted *as essentially* self-destructive. Such behavior was most *frequently exhibited* when major life adjustments had to be made

and was more likely to occur when the emotional and socio-economic environment was suboptimal. (129)

Etzwiler and Sines in their survey of juvenile diabetes reported rebellious and resentful behavior in 12 per cent of their cases (39)

Sterky undertook a study to find out whether diabetic children have an increased frequency of emotional disturbances and, if so what factors in the diabetic state might have influenced the symptoms His group of diabetic children had a significantly increased frequency of psychologically disturbed mothers who chiefly displayed various anxiety symptoms The frequency of children without reported psychological symptoms was the same in the diabetic as in the nondiabetic control group School achievements were found to be equal in the two groups and were not influenced by the age at the onset of diabetes Cases with "poor" diabetic control were found to have psychological symptoms more often than those with fair control. (132)

Knowles and his co-workers reported that thirteen of ninety two juvenile diabetics exhibited an excessive drive for self assertion. They rebelled against authority over ate were self-destructive and went to great lengths to attract attention. It seemed as if diabetes aggravated the usual teen-age drive for recognition. Hostility was first directed towards parents and later towards teachers and employers. Job-holding was frequently difficult. Another group of thirteen patients suffered from severe hidden anxiety They had great difficulty in accepting the fact that they had diabetes and, consequently denied the disease. (81)

Hinkle and co-workers in a panel discussion stated that the impact of diabetes mellitus on the younger child is at first purely physical because getting an injection hurts As the child becomes older the so-called stigma" of being a diabetic becomes increasingly significant and attempts are made to keep the condition secret The panel members thought that girls were more likely to be secretive in this respect (65)

Fischer pinpoints the factors which were found to be most important as causes of emotional disturbance in a group of diabetic children. These were 1) dietary restrictions 2) the need for insulin injections 3) urinalysis, 4) the limitations of the daily activities that diet and insulin impose 5) the stigma of being a diabetic, 6) the future outlook for a diabetic child (development of complications cardiovascular neurologic renal) In his opinion diabetic children do not seem to do as well in school and do not achieve success in college or professional training although it cannot be stated definitely whether this is due to physical or psychological factors. There are, of course, exceptions to this general pattern of achievement. (45)

Greenberg and Blair pointed out the numerous difficulties in the treatment of childhood diabetes The emotional difficulties seem to arise from the presence of the diabetes and the effect this has on family relationships as well as on the child himself (53)

Falstein and Judas reported the treatment of two juvenile diabetics and demonstrated the development of a highly pathologic mother-child relationship resulting from the diabetic management. They emphasized the need for a multidisciplinary approach to the problems of diabetics. (42)

Davis and co-workers attempted to evaluate the attitude of children with diabetes mellitus and its treatment. Their findings suggest that diabetic boys and girls may consider their disorder a normal part of their lives without really comprehending its seriousness The fact that the impact of having a serious long-term illness either was not fully recognized or was "successfully denied, by this group of children was demonstrated by their preference for diabetes over *several far less serious conditions, e.g.,* constipation acne or obesity (30)

Psychological research on childhood diabetes mellitus

Brown in 1938 in his group of diabetic children found no significant deviation in intelligence from that of their sibling controls or from the average of Minneapolis children (as determined by Stanford-Binet test) (15)

More recently studies of the childhood diabetic personality by Kubany and co-workers (83) and of their mental health by Sterky (132) revealed no average changes from normal. On the other hand Swift and Seidman employing both psychologic and psychiatric methods presented evidence of deviation from the normal (134) Ack and Weil found a significant negative difference in the Stanford-Binet intelligence

scale scores of diabetics as compared with their siblings, but only in children who had acquired the disease before the age of five years. The authors suggest two possible explanations.

1 *Physiologically* the brain tissues of the young diabetic patient may be impaired by metabolic disturbances which do not produce brain damage in older diabetic children.

2 *Psychologically* the impact of the realization of chronic disease on the young child' immature ego may result in some loss of IQ (1)

Weil and Ack reported on school achievement in cases of juvenile diabetes mellitus. They compared diabetic children with their non-diseased siblings in regard to their scholastic achievements and related the results to their previously determined intelligence quotients. They found tha the diabetic children as well as their siblings had achievement scores which were not significantly different from what might be expected with their intelligence quotients. There was no difference from their siblings in the achievement levels of the diabetic children, either as a single group or when classified on the basis of age at onset or duration of the disease. They concluded that the etiology of the school problems was not related to scholastic achievement. (146)

and was more likely to occur when the emotional and socio-economic environment was suboptimal. (129)

Etzwiler and Sines in their survey of juvenile diabetes reported rebellious and resentful behavior in 12 per cent of their cases (39)

Sterky undertook a study to find out whether diabetic children have an increased frequency of emotional disturbances and, if so what factors in the diabetic state might have influenced the symptoms. His group of diabetic children had a significantly increased frequency of psychologically disturbed mothers who chiefly displayed various anxiety symptoms. The frequency of children without reported psychological symptoms was the same in the diabetic as in the nondiabetic control group School achievements were found to be equal in the two groups and were not influenced by the age at the onset of diabetes Cases with "poor" diabetic control were found to have psychological symptoms more often than those with fair" control. (132)

Knowles and his co-workers reported that thirteen of ninety two juvenile diabetics exhibited an excessive drive for self assertion. They rebelled against authority over ate were self-destructive and went to great lengths to attract attention. It seemed as if diabetes aggravated the usual teen-age drive for recognition. Hostility was first directed towards parents and later towards teachers and employers. Job-holding was frequently difficult Another group of thirteen patients suffered from severe hidden anxiety They had great difficulty in accepting the fact that they had diabetes and consequently denied the disease. (81)

Hinkle and co-workers in a panel discussion stated that the impact of diabetes mellitus on the younger child is at first purely physical because getting an injection hurts. As the child becomes older the so-called stigma of being a diabetic becomes increasingly significant and attempts are made to keep the condition secret The panel members thought that girls were more likely to be secretive in this respect (65)

Fischer pinpoints the factors which were found to be most important as causes of emotional disturbance in a group of diabetic children. These were 1) dietary restrictions 2) the need for insulin injections 3) urinalysis 4) the limitations of the daily activities that diet and insulin impose 5) the stigma of being a diabetic, 6) the future outlook for a diabetic child (development of complications cardiovascular neurologic renal) In his opinion, diabetic children do not seem to do as well in school and do not achieve success in college or professional training although it cannot be stated definitely whether this is due to physical or psychological factors. There are of course, exceptions to this general pattern of achievement. (45)

Greenberg and Blair pointed out the numerous difficulties in the treatment of childhood diabetes. The emotional difficulties seem to arise from the presence of the diabetes and the effect this has on family relationships as well as on the child himself (53)

Falstein and Judas reported the treatment of two juvenile diabetics and demonstrated the development of a highly pathologic mother-child relationship resulting from the diabetic management. They emphasized the need for a multidisciplinary approach to the problems of diabetics. (42)

Davis and co-workers attempted to evaluate the attitude of children with diabetes mellitus and its treatment. Their findings suggest that diabetic boys and girls may consider their disorder a normal part of their lives without really comprehending its seriousness The fact that the impact of having a serious long-term illness either was not fully recognized, or was "successfully denied by this group of children was demonstrated by their preference for diabetes over several far less serious conditions e.g., constipation acne or obesity (30)

Psychological research on childhood diabetes mellitus

Brown in 1938 in his group of diabetic children, found no significant deviation in intelligence from that of their sibling controls or from the average of Minneapolis children (as determined by Stanford-Binet test) (15)

More recently studies of the childhood diabetic personality by Kubany and co-workers (83) and of their mental health by Sterky (132) revealed no average changes from normal. On the other hand Swift and Seidman employing both psychologic and psychiatric methods presented evidence of deviation from the normal (134) Ack and Weil found a significant negative difference in the Stanford Binet intelligence

During the gathering of the series it soon became evident that the number of diabetically well controlled cases in the clinic population exceeded the number of poorly controlled cases. Because of this, all poorly controlled cases which were hospitalized during the study were included in the material. There were 28 such cases. 2 cases (Nos. 16 and 53) were added to the material from the out-patient clientele because in these cases, Mauriac syndrome was a sign of poor diabetic control. There were altogether 5 cases in the P group diagnosed as Mauriac's syndrome.

Mauriac's syndrome, consisting of dwarfism, hepatomegaly and obesity is without exception connected with poor diabetic control (41).

Of the diabetically well controlled children, 27 were hospitalized during the time of the study either for diabetes or for some other illness, and the remaining 3 (Nos. 3, 50 and 56) were added to the material from the out-patient clientele, being selected to match for age and sex as closely as possible the P group.

METHODS

1 Int rvi w the pa e t

If the child was hospitalized, the interviews with the parent( ) were usually arranged through the hospital personnel at a convenient time, usually before or after the regular visiting hours. If the child was visiting the out-patient clinic, the author sent a letter in advance to the parent, usually the mother, asking for her co-operation in the study. If the parent did not answer the first call he usually responded to the second. *Finally, not a single case had to be excluded* because of poor co-operation.

The mothers (in 47 cases), the *fathers* (in 4 cases) or both parents (in 9 cases) were interviewed by the author. Of the 59 possible cases (*the mother of one of the poorly controlled* children was deceased) the mothers of 3 children could not be reached. These were all cases in which the father alone was responsible for bringing the child to the hospital or to the out-patient clinic. The reason for the mother's absence was

a) in two cases the care of younger siblings and
b) in one case the mother's working hours away from home

The number of interviews ranged from one to twelve. In those cases where the parent (s) was seen only once, a special questionary was gone through. This questionary is presented as one of the Appendixes to this thesis. In those cases in which the parent(s) was seen more than once, the same questionary was gone through usually during the last interview in order to get comparable data from the interviews.

2. Interviewing the child

If the child was hospitalized, the time for the interview was arranged so as not to disturb other ward activities. If the child visited the out-patient clinic the author sent a letter in advance to the parents or to the child, asking for an *interview*.

Every child had at least one psychiatric interview or play observation by the author. The interview technique with the children was relatively nondirective. If the child suffered from marked separation anxiety the parents were allowed to be present in the interviewing room for a few minutes. The younger children were introduced to von Staabs Sceno-material or drawing equipment. The older children could choose between drawing and talk. In those cases where the child chose either play or drawing, this was followed by a period of discussion. During this discussion the reason for the child' coming to *the interview, his feelings and thoughts about his* diabetes, and his eating habits were touched upon.

Table 2 A. shows the number of interviews with parents in the GF and P groups respectively.

Tabl 2 A. Number of interviews with parents.

	GF	P	Total
1 interview with the mother	9	9	18
2 or 3 interv ew with the mother	13	11	24
4 or more interviews with the mother	3	3	6
1 interview with the *father*	—	2	2
2 or 3 interviews with the father	1	1	2
1 interview with the mother + 1 *interview* with the *father*	1	2	3
interviews with the mother + 2 interviews with both parents	1	—	1
3 interviews with the mother + 1 interview with the f ther	—	1	1
4 or more interviews with the mother + 1 interview with the f ther	1	1	
3 interviews with both parents	1	—	1
[illegible]	[illegible]	[illegible]	[illegible]

Material and methods

MATERIAL

The series collected consisted of 60 diabetic children all attending th. diabetic out patient clinic of the Children s Hospital University of Turku The patients visiting this University Hospital come mainly from Turku and the surrounding small towns and country communities The total out patient diabetic population as to December 31 1967 was 176 patients Thus this series represents roughly one-third of the total number

Gathering of the series took place between September 1964 and December 1967 The cases were selected on the basis of the following criteria

1 *Age* Children under 5 years of age at the time of the psychological examination were excluded because of the difficulty of giving and analyzing the psychological tests

2 *Duration of the disease* Since the purpose of the study was to examine the parent s coping processes and the children s later adjustment it was decided to confine the series *to children* who at the time of the last examination, had been diagnosed as diabetic for at least *one year*

3 *The diabetic control* All cases over five years of age in whom diabetes had been diagnosed at least one year previously were classified into two groups in terms of diabetic control

a. Good or Fair Control (abbreviated as GF)
b Poor Control (abbreviated as P)

The criteria for diabetic control closely resemble those of Gamstorp and co-workers (48) and are presented in Table 1 To be considered GF the patients had to meet four of the five criteria listed below in Table 1 Correspondingly to be considered P the patients had to meet four of the five criteria listed in Table 1

Table 1 *The criteria for adequacy of diabetic control*

	GF	P
Growth	Normal or greater than the tenth percentile for age	Below the tenth percentile for age
Acetonuria	Urine free of acetone 50 to 75 per cent of the samples collected	Acetonuria more than 50 per cent of the samples collected
24-hour urine glucose	Less than 30 g	Greater than 30 g
Fasting blood sugar level	Up to 200 mg per 100 ml	More than 200 mg per 100 ml.
Number of hospitalizations per year for control of diabetes	No more than one hospitalization per year	More than one hospitalization per year

Growth The height at the time of the last examination was compared with the normal values for Finnish children published by the Center for Study in Child Growth and Development (74)

Acetonuria The urine was tested for acetone each time the child visited the out patient clinic In addition to this the urinalysis for acetone (a tape test) was performed at home every morning or every other morning and the results written down in a notebook which the child then brought with him to the clinic

24 hour quantitative urine glucose This was measured each time the child visited the out patient clin'c.

During the gathering of the series it soon became evident that the number of diabetically well controlled cases in the clinic population exceeded the number of poorly controlled cases. Because of this, all poorly controlled cases which were hospitalized during the study were included in the material. There were 28 such cases. 2 cases (Nos. 16 and 53) were added to the material from the out-patient clientele because, in these cases, Mauriac's syndrome was a sign of poor diabetic control. There were altogether 5 cases in the P group diagnosed as Mauriac's syndrome.

Mauriac syndrome, consisting of dwarfism, hepatomegaly and obesity is without exception connected with poor diabetic control (41).

Of the diabetically well controlled children 27 were hospitalized during the time of the study either for diabetes or for some other illness and the remaining 3 (Nos 3 50 and 56) wer added to the materia from the out-patient clientele, being selected to match for ge and sex as closely as possible the P group

METHODS

1 I te i w g th p nt

It the child was hospitalized, the interviews with the parent( ) were usually arranged through the hospital personnel at a convenient time usually before or after the regular visiting hours If the child was visiting the out-patient clinic, the author sent letter in advance to the parent usually the mother asking for her co-operation in the study If the parent did not answer the first call he usually responded to the second. Finally not a single case had to be excluded because of poor co-operation.

The mothers (in 47 cases) the fathers (in 4 cases) or both parents (in 9 cases) were inter iewed by the author Of the 59 possible cases (the mother of one of the poorly controlled children was deceased) the mothers of 3 children could not be reached These were all cases in which the father alone was responsible for bringing the child t the hospital or to the out patient clinic The reason for the mother absence was

) In two cases the care of younger siblings and
b) In one case the mother working hours away from home.

The number of interviews ranged from one to twelve In those cases where the parent ( ) was seen only once, a special questionary was gone through. This questionary is presented as one of the Appendixes to this thesis. In those cases in which the parent( ) was seen more than once, the same questionary was gone through usually during the last interview in order to get comparable data from the interviews.

2. Int r iewing the child

If the child was hospitalized, the time for the interview was arranged so as not to disturb other ward activities. If the child visited the out patient clinic the author sent letter in advance to the parents or to the child asking for an interview

Every child had at least one psychiatric interview or play observation by the author The interview technique with the children was relatively nondirective. If the child suffered from marked separation anxiety the parents were allowed to be present in the interviewing room for few minutes. The younger children were introduced to von Staabs Scenomaterial or drawing equipment. The older children could choose between drawing and talk. I those cases where the child chose either play or drawing, this was followed by period of discussion. During this discussion the reason for the child coming to the interview his feelings and thoughts about his diabetes and his eating habits were touched upon.

Table 2 A. shows the number of interviews with parents in the GF and P groups respectively

Table 2 A Number of interviews with parents.

	GF	P	Total
1 interview with the mother	9	9	18
2 or 3 interviews with the mother	13	11	24
4 or more interviews with the mother	3	3	6
1 interview with the father	—	2	2
2 or 3 interviews with the father	1	1	2
1 interview with the mother + 1 interview with the father	1	2	3
2 interviews with the mother + 2 interviews with both parents	1	—	1
3 interviews with the mother + 1 interview with the f ther	—	1	1
4 or more interviews with the mother + 1 interview with the father	1	1	
3 interviews with both parents	1	—	1
	30	30	60

Material and methods

MATERIAL

The series collected consisted of 60 diabetic children all attending th diabetic out-patient clinic of the Children s Hospital University of Turku The patients visiting this University Hospi tal come mainly from Turku and the surrounding small towns and country communities The total out patient diabetic population as to December 31 1967 was 176 patients. Thus this series represents roughly one third of the total number

Gathering of the series took place between September 1964 and December 1967 The cases were selected on the basis of the following criteria

1 *Age* Children under 5 years of age at the time of the psychological examination were excluded because of the difficulty of giving and analyzing the psychological tests

2 *Duration of the disease* Since the purpose of the study was to examine the parent s coping processes and the children s later adjustment it was decided to confine the series to children who at the time of the last examination, had been diagnosed as diabetic for at least one year

3 *The diabetic control* All cases over five years of age, in whom diabetes had been diagnosed at least one year previously were classified into two groups in terms of diabetic control

a. Good or Fair Control (abbreviated as GF)
b Poor Control (abbreviated as P)

The criteria for diabetic control closely resemble those of Gamstorp and co-workers (48) and are presented in Table 1 To be considered GF the patients had to meet four of the five criteria listed below in Table 1 Correspondingly to be considered P the patients had to meet four of the five criteria listed in Table 1

Table 1 *The criteria for adequacy of diabetic control*

	GF	P
Growth	Normal or greater than the tenth percentile for age	Below the tenth percentile for age
Acetonuria	Urine free of acetone 50 to 75 per cent of the samples collected	Acetonuria more than 50 per cent of the samples collected
24-hour urine glucose	Less than 30 g	Greater than 30 g
Fasting blood sugar level	Up to 200 mg per 100 ml	More than 200 mg per 100 ml
Number of hospitalizations per year for control of diabetes	No more than one hospitalization per year	More than one hospitalization per year

Growth The height at the time of the last examination was compared with the normal values for Finnish children published by the Center for Study in Child Growth and Development (74)

Acetonuria. The urine was tested for acetone each time the child visited the out-patient clinic. In addition to this the urinalysis for acetone (a tape test) was performed at home every morning or every other morning and the results written down in a notebook which the child then brought with him to the clinic

24-hour quantitative urine glucose This was measured each time the child visited the out patient clin c.

During the gathering of the series it soon became evident that the number of diabetically well controlled cases in the clinic population exceeded the number of poorly controlled cases. Because of this all poorly controlled cases which were hospitalized during the study were included in the material. There were 28 such cases. 2 cases (Nos. 16 and 53) were added to the material from the out-patient clientele because, in these cases Mauriac's syndrome was a sign of poor diabetic control. There were altogether 5 cases in the P group diagnosed as Mauriac's syndrome.

Mauriac syndrome, consisting of dwarfism, hepatomegaly and obesity is without exception connected with poor diabetic control (41).

Of the diabetically well controlled children 27 were hospitalized during the time of the study either for diabetes or for some other illness and the remaining 3 (Nos. 3, 50 and 56) were added to the material from the out-patient clientele, being selected to match for age and sex as closely as possible the P group.

METHODS

1. Interviewing the parents

If the child was hospitalized, the interviews with the parent( ) were usually arranged through the hospital personnel at a convenient time usually before or after the regular visiting hours. If the child was visiting the out-patient clinic, the author sent a letter in advance to the parent, usually the mother asking for her co-operation in the study. If the parent did not answer the first call he usually responded to the second. Finally not a single case had to be excluded because of poor co-operation.

The mothers (in 47 cases), the fathers (in 4 cases) or both parents (in 9 cases) were interviewed by the author. Of the 59 possible cases (the mother of one of the poorly controlled children was deceased) the mothers of 3 children could not be reached. These were all cases in which the father alone was responsible for bringing the child to the hospital or to the out-patient clinic. The reason for the mother's absence was

a) in two cases the care of younger siblings and
b) in one case the mother's working hours away from home.

The number of interviews ranged from one to twelve. In those cases where the parent (s) was seen only once a special questionary was gone through. This questionary is presented as one of the Appendices to this thesis. In those cases in which the parent( ) was seen more than once, the same questionary was gone through usually during the last interview in order to get comparable data from the interviews.

2. Interviewing the child

If the child was hospitalized, the time for the interview was arranged so as not to disturb other ward activities. If the child visited the out-patient clinic the author sent a letter in advance to the parents or to the child asking for an interview.

Every child had at least one psychiatric interview or play observation by the author. The interview technique with the children was relatively nondirective. If the child suffered from marked separation anxiety the parents were allowed to be present in the interviewing room for a few minutes. The younger children were introduced to von Staabs Sceno-material or drawing equipment. The older children could choose between drawing and talk. In those cases where the child chose either play or drawing, this was followed by a period of discussion. During this discussion the reason for the child's coming to the interview, his feelings and thoughts about his diabetes and his eating habits were touched upon.

Table 2 A. shows the number of interviews with parents in the GF and P groups respectively.

Table 2 A. Number of interviews with parents.

	GF	P	Total
1 interview with the mother	9	9	18
2 or 3 interviews with the mother	13	11	24
4 or more interviews with the mother	3	3	6
1 interview with the father	—	2	2
2 or 3 interviews with the father	1	1	2
1 interview with the mother + 1 interview with the father	1	2	3
2 interviews with the mother + 2 interviews with both parents	1	—	1
3 interviews with the mother + 1 interview with the father	—	1	1
4 or more interviews with the mother + 1 interview with the father	1	1	
3 interviews with both parents	1	—	1
	30	30	60

Table 2 B shows the number of interviews with the children in the GF and P groups respectively

Table 2 B Number of interviews with the children

	GF	P	Total
1 interview with the child	12	10	22
2 or 3 interviews with the child	13	17	30
4 or more interviews	5	3	8
	30	30	60

The average number of interviews per family was 4.2

3 Supplementary information

The information obtained in the interviews was supplemented by the hospital records and records from the out patient clinic 6 children had received treatment at other hospitals. In these cases the records of these hospitals were placed at the author s disposal.

During the children s hospital stays the author had weekly conferences with the occupational therapist who observed the children in group situations

4 Psychological tests

Three psychological tests were administered to all the children an intelligence test (Terman-Merrill Lehtovaara) and two projective techniques — the Rosenzweig Picture Frustration Test and the Holzman Inkblot Technique Two psychologists performed the psychological testing of the children. One of them conducted all the Holzman Inkblot Tests all the Rosenzweig Picture Frustration tests and 33 of the intelligence tests The other psychologist conducted the intelligence tests in 26 cases One of the patients had undergone a psychological test with a third psychologist at the time of the investigation. Because the test result was available to the author it was felt unnecessary to repeat that child s intelligence test The external conditions in which the testing was carried out were standardized as possible in the same room at the hospital. There were four exceptions to this two children were tested at their schools one at his home and the fourth in the community s public health clinic All were children who visited the out patient clinic very infrequently and reaching them out in their own home communities considerably shortened the time of the investigation.

The examinations were conducted in two sessions each lasting approximately one hour The psychologists did not know at the time of the examination, which diabetic group the child belonged to

5 Teacher s assessment

With the permission of the parent, a questionary was sent to the child s teacher in every case in which the child attended school. This questionary is presented in the "Appendixes of this paper The teacher was asked to evaluate the child s school achievement and some aspects of the child s behavior at school. Teacher participation was exceptionally good. All teachers responded in a matter of several days or a few weeks either returning the completed questionary or contacting the author by phone.

6 Statistical methods

The statistical methods employed on the medical social and sociopsychiatric data were limited to statistical hypothesis testing The data of these parts of the research were in most cases classificatory or measured in an ordinal scale. This fact led to the use of nonparametric methods (in this case the chi test) Parametric tests were chosen only in two cases (t test for data in Tables 3 and 4)

The test used in calculating the Rosenzweig Picture Frustration results was the *t* test.

For the analysis of the Holzman Inkblot Technique scores the method of Discrimination Analysis was used In this method the position of every subject is estimated in relation to the line that best separates the two groups Mahalanobis D^2 ans associated *F* statistics were computed to test the group differences Because the scores are frequency counts of responses they were assumed to approach the Poisson distribution. The Freeman-Tukey square root transformation was used as suggested by Mosteller and Bush (100) That is $z = \sqrt{X} + \sqrt{X+1}$ where X is the observed frequency score

The analysis was computed at the Northern Europe University Computing Center Lyngby Denmark, (Proj No 403026) using the BDM 04M computer program

CHARACTERISTICS OF THE SERIES

Age distribution. Figure 1 shows the age distribution of the patients at the time of the last examination.

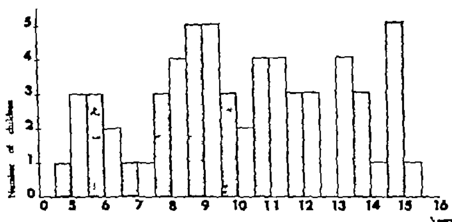


Fig. 1 Age distribution at the time of the last examination (years) in the GF group (white bars) and in the P group (shaded bars)

Average age at the time of the last examination was 11 yrs 4 mons in the GF group and 10 yrs 8 mos in the P group.

Sex distribution. There were 14 boys and 16 girls in the GF group and 15 boys and 15 girls in the P group.

Place of residence. Table 2 shows the place of residence of the patients in the GF group and the P group respectively.

Table 2. Place of residence.

Place of residence	GF	P	Total
Turku	6	6	12
Country town	6	7	13
Country community	18	17	35
	30	30	60

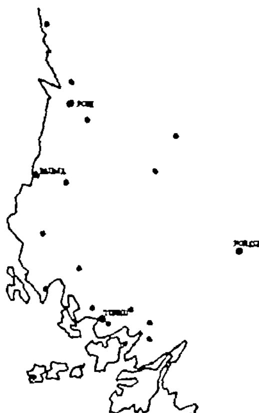


Figure 2 shows the map of the area in South-West Finland served by our Children Hospital

Figure 2 Map of South-West Finland

Table 2 B shows the number of interviews with the children in the GF and P groups respectively

Table 2 B Number of interviews with the children

	GF	P	Total
1 interview with the child	12	10	22
2 or 3 interviews with the child	13	17	30
4 or more interviews	5	3	8
	30	30	60

The average number of interviews per family was 4 2

3 Supplementary information

The information obtained in the interviews was supplemented by the hospital records and records from the out patient clinic 6 children had received treatment at other hospitals. In these cases the records of these hospitals were placed at the author s disposal

During the children s hospital stays the author had weekly conferences with the occupational therapist who observed the children in group situations.

4 Psychological tests

Three psychological tests were administered to all the children an intelligence test (Terman-Merrill Lehtovaara) and two projective techniques — the Rosenzweig Picture Frustration Test and the Holzman Inkblot Technique. Two psychologists performed the psychological testing of the children One of them conducted all the Holzman Inkblot Tests all the Rosenzweig Picture Frustration tests and 33 of the intelligence tests The other psychologist conducted the intelligence tests in 26 cases One of the patients had undergone a psychological test with a third psychologist at the time of the investigation. Because the test result was available to the author it was felt unnecessary to repeat that child s intelligence test. The external conditions in which the testing was carried out were standardized as possible in the same room at the hospital There were four exceptions to this two children were tested at their schools one at his home and the fourth in the community s public health clinic. All were children who visited the out patient clinic very infrequently and reaching them out in their own home communities considerably shortened the time of the investigation.

The examinations were conducted in two sessions each lasting approximately one hour The psychologists did not know at the time of the examination, which diabetic group the child belonged to

5 Teacher s assessment

With the permission of the parent a questionary was sent to the child s teacher in every case in which the child attended school. This questionary is presented in the Appendixes of this paper The teacher was asked to evaluate the child's school achievement and some aspects of the child s behavior at school. Teacher participation was exceptionally good. All teachers responded in a matter of several days or a few weeks either returning the completed questionary or contacting the author by phone.

6 Statistical methods

The statistical methods employed on the medical social and sociopsychiatric data were limited to statistical hypothesis testing The data of these parts of the research were in most cases classificatory or measured in an ordinal scale. This fact led to the use of nonparametric methods (in this case the chi-test) Parametric te ts were chosen only in two cases (t test for data in Tables 3 and 4)

The test used in calculating the Rosenzweig Picture Frustration results was the t test

For the analysis of the Holzman Inkblot Technique scores the method of Discrimination Analysis was used. In this method the position of every subject is estimated in relation to the line that best separates the two groups Mahalanobis D^2 ans associated F-statistics were computed to test the group differences Because the scores are frequency counts of responses they were assumed to approach the Poisson distribution. The Freeman-Tukey square-root transformation was used as suggested by Mostseller and Bush (100) That is $z = \sqrt{X} + \sqrt{X+1}$ where X is the observed frequency score.

The analysis was computed at the Northern Europe University Computing Center Lyngby Denmark (Proj No 403026) using the BDM 04M computer program.

Duration of illness

Table 4 shows the duration of diabetes in the cases of the series.

Table 4 Duration of illness.

Duration of diabetes	GF	P	Total
1 yr to 1 yr 11 mo	6	2	8
2 yrs to 2 yrs 11 mo	12	4	16
3 yrs to 3 yrs 11 mo	5	4	9
4 yrs to 4 yrs 11 mo	3	3	6
5 yrs to 5 yrs 11 mo	2	7	9
6 yrs to 6 yrs 11 mo	1	—	1
7 yrs to 7 yrs 11 mo	—	4	4
8 yrs to 8 yrs 11 mo	—	3	3
9 yrs to 9 yrs 11 mo	—	2	2
10 yrs to 10 yrs 11 mo	1	—	1
11 yrs to 11 yrs 11 mo	—	1	1
	30	30	60

Average duration of the illness in the GF group was 3 yrs 3 mos and in the P group 5 yrs 5 mo There is a significant difference between the groups ($p<0.05$)

Duration of diabetes is also shown in Figure 4

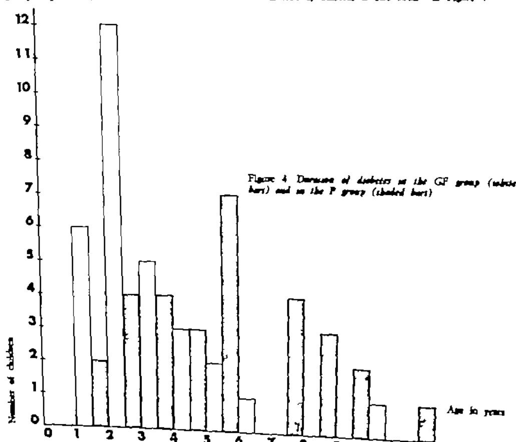


Figure 4 Duration of diabetes in the GF group (white bars) and in the P group (shaded bars)

Results

1 Medical data

Table 3 shows the age *at the diagnosis of diabetes*

Table 3 Age at the diagnosis of diabetes.

Age at diagnosis	GF	P	Total
2 yrs to 2 yrs 11 mo	—	7	7
3 yrs to 3 yrs 11 mo	5	4	9
4 yrs to 4 yrs 11 mo	1	6	7
5 yrs to 5 yrs 11 mo	1	1	2
6 yrs to 6 yrs 11 mo	3	4	7
7 yrs to 7 yrs 11 mo	6	4	10
8 yrs to 8 yrs 11 mo	3	—	3
9 yrs to 9 yrs 11 mo	3	1	4
10 yrs to 10 yrs 11 mo	1	2	3
11 yrs to 11 yrs 11 mo	4	—	4
12 yrs to 12 yrs 11 mo	2	—	2
13 yrs to 13 yrs 11 mo	—	1	1
14 yrs to 14 yrs 11 mo	1	—	1
	30	30	60

Average age at the diagnosis in the G F group was 8 yrs 1 mo and in the P group 5 yrs 5 mo There is a statistically significant difference between the groups ($p<0.02$)

This is in accordance with the general observation that diabetes is more difficult to control in the young child than in the older child

In the cases of this series all the children who had developed diabetes prior to the age of three years have poor control of their illness.

Age at diagnosis also shown Figure 3

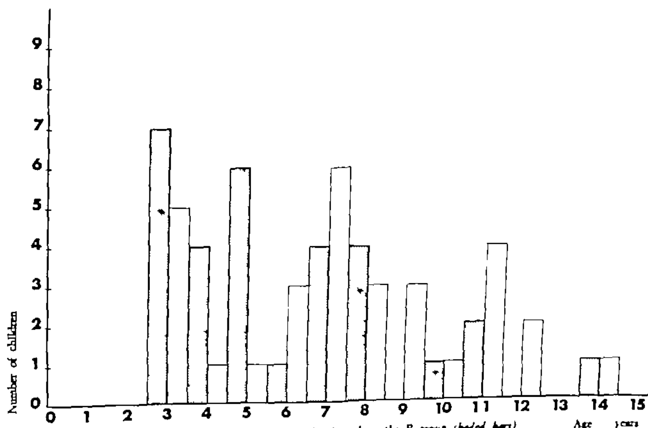


Figure 3 *Age at diagnosis in the GF group (white bars) and in the P group shaded bars)*

Duration of illness

Table 4 shows the duartion of diabetes in the cases of the series.

Table 4 Duration of illness.

Duration of diabetes	GF	P	Total
1 yr to 1 y 11 mo	6	2	8
2 yrs to 2 yrs 11 mo	12	4	16
3 yrs to 3 yrs 11 mo	5	4	9
4 yrs to 4 yrs 11 mo	3	3	6
5 yrs to 5 yrs 11 mo	2	7	9
6 yrs to 6 yrs 11 mo	1	—	1
7 yrs to 7 yrs 11 mo	—	4	4
8 yrs to 8 yrs 11 mo	—	3	3
9 yrs to 9 yrs 11 mo	—	2	2
10 yrs to 10 yrs 11 mo	1	—	1
11 yrs to 11 yrs 11 mo	—	1	1
	30	30	60

Average duration of the illness in the GF group was 3 yrs 3 mos and in the P group 5 yrs 5 mo. There is significant difference between the groups ($p<0.05$)

Duration of diabetes is also shown in Figure 4

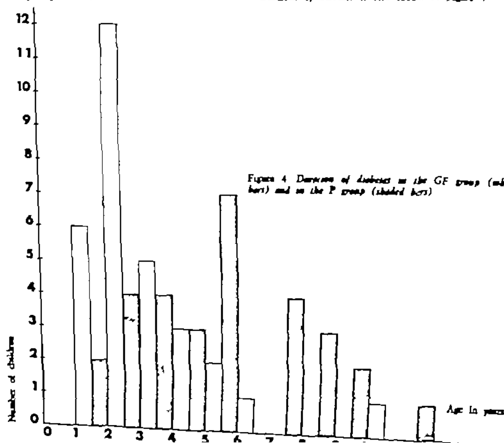


Figure 4 Duration of diabetes in the GF group (white bars) and in the P group (shaded bars)

Results

1 Medical data

Table 3 shows the age *at the diagnosis of diabetes*

Table 3 Age at the diagnosis of diabetes

Age at diagnosis	GF	P	Total
2 yrs to 2 yrs 11 mo	—	7	7
3 yrs to 3 yrs 11 mo	5	4	9
4 yrs to 4 yrs 11 mo	1	6	7
5 yrs to 5 yrs 11 mo	1	1	2
6 yrs to 6 yrs 11 mo	3	4	7
7 yrs to 7 yrs 11 mo	6	4	10
8 yrs to 8 yrs 11 mo	3	—	3
9 yrs to 9 yrs 11 mo	3	1	4
10 yrs to 10 yrs 11 mo	1	2	3
11 yrs to 11 yrs 11 mo	4	—	4
12 yrs to 12 yrs 11 mo	2	—	2
13 yrs to 13 yrs 11 mo	—	1	1
14 yrs to 14 yrs 11 mo	1	—	1
	30	30	60

Average age at the diagnosis in the G F group was 8 yrs 1 mo and in the P group 5 yrs 5 mo. There is a statistically significant difference between the groups ($p<0.02$)

This is in accordance with the general observation that diabetes is more difficult to control in the young child than in the older child.

In the cases of this series all the children who had developed diabetes prior to the age of three years have poor control of their illness.

Age at diagnosis is also shown in Figure 3

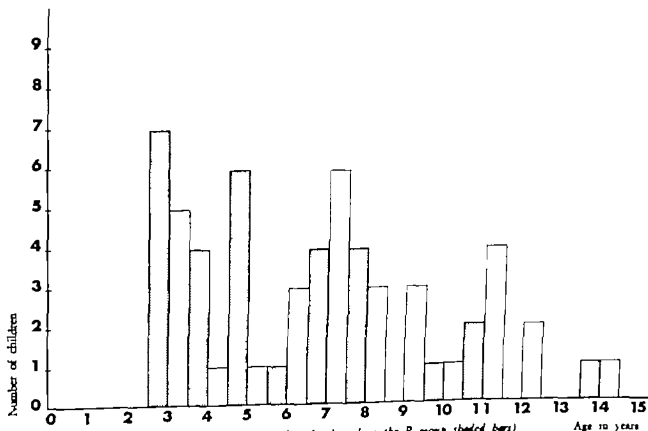


Figure 3 *Age at diagnosis in the GF group (white bars) and in the P group shaded bars)*

Duration of illness

Table 4 shows the duartion of diabetes in the cases of the series.

Table 4 Duration of illness.

Duration of diabetes	GF	P	Total
1 yr to 1 yr 11 mo	6	2	8
2 yrs to 2 yrs 11 mo	12	4	16
3 yrs to 3 yrs 11 mo	5	4	9
4 yrs to 4 yrs 11 mo	3	3	6
5 yrs to 5 yrs 11 mo	2	7	9
6 yrs to 6 yrs 11 mo	1	—	1
7 yrs to 7 yrs 11 mo	—	4	4
8 yrs to 8 yrs 11 mo	—	3	3
9 yrs to 9 yrs 11 mo	—	2	2
10 yrs to 10 yrs 11 mo	1	—	1
11 yrs to 11 yrs 11 mo	—	1	1
	30	30	60

Average duration of the illness in the GF group was 3 yrs 3 mos and in the P group 5 yrs 5 mo. There is significant difference between the groups ($p<0.05$)

Duration of diabetes is also shown in Figure 4.

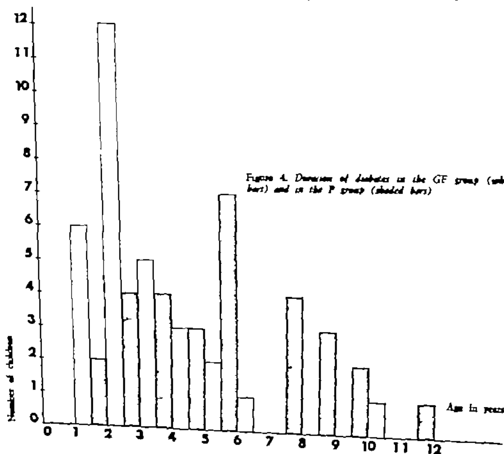


Figure 4. *Duration of diabetes in the GF group (white bars) and in the P group (shaded bars)*

Heredity

Table 5 shows the occurrence of known cases of diabetes among the relatives of the children of the two groups

Table 5 Relatives with diabetes

	GF	P	Total
Diabetes in first degree relatives	8	14	22
Diabetes in more distant relatives	8	7	15
No known diabetic relatives	14	9	23
	30	30	60

The term first degree relatives in this study includes the patient s siblings parents grand parents and first cousins There is no statistically significant difference between the groups

The series included six families in which *more than one child is affected with diabetes* Table 6 shows these cases distributed according to diabetic control

Table 6 Diabetic control in siblings

Number of families	GF	P	Ungrouped	Total
6	3	7	3	13

These six families as is shown in Table 6 have altogether 13 diabetic children Of these 13 children 9 are included in the material.

Four are excluded for the following reasons in two cases the diabetes was of less than one year s duration In another case the child was so young that it was not possible to give her psychological tests used in this study and in the remaining case the patient was over fifteen years old at the time of the study

Growth

In the present investigation the data on height at the time of diagnosis of diabetes and at the time of the last examination have been obtained These figures have been compared with the normal values for Finnish children published by the Center for Study in Child Growth and Development (74) Table 7 shows the comparative heights at the time of diagnosis for the GF and the P groups respectively

Table. 7 Height at the diagnosis of diabetes.

	GF	P	Total
Height above normal	3	—	3
normal	26	30	56
" below normal	1	—	1
	30	30	60

Table 8 shows the heights of the two groups at the time of the last investigation.

Table 8 Height at the time of the last investigation

	GF	P	Total
Height above normal	—	—	—
normal	29	23	52
below normal	1	7	8
	30	30	60

The frequency of stunted growth at the time of the last examination in the series is 13.3 % (3 3 % in the GF group and 23.3 % in the P group)

The figures presented in Tables 7 and 8 are too small for statistical treatment Moreover they cannot be considered as final figures because the majority of the patients have not yet reached adult stature There is however a tendency for the heights to be below the lower normal limit in the P group In the GF group there is only on. child whose height at the time of the last investigation was below normal This is the same child whose height was already below the lower normal limit at the diagnosis of diabetes (Table 7) Th growth retardation observed in the P group may thus in some way be connected with the control of the diabetes.

2 Social and socio psychiatric data

Size of the family

Table 9 shows the total number of children in the families of the GF and the P groups rerpectively

Table 9 Total number of children.

Number of children	GF	P	Total
1 child	2	5	7
2 children	8	4	12
3 children	9	7	16
4 to 5 children	4	6	10
6 to 8 children	6	8	14
9 to 11 children	1	—	1
	30	30	60

Birth rank

Table 10 shows the birth rank of diabetic children in the GF and the P groups respectively

Table 10 Birth rank.

	GF	P	Total
Only child	2	5	7
Youngest child	8	9	17
Eldest child	11	3	14
Middle child	9	13	22
	30	30	60

According to these findings it is relatively rare for an eldest child's diabetes to be poorly controlled. Of the 14 diabetic eldest children in the series 11 were well or fairly controlled, whereas only 3 were poorly controlled. The difference is statistically almost significant ($p < 0.10$) (In the statistical calculation the "only child" category has been omitted.) The reason for this can not be stated categorically but we may speculate that it is psychological. The reason may be suggested to be the responsibility placed upon the eldest child in the family an attitude which he carries over to the care of his disease. Two of the three poorly controlled eldest children developed diabetes during the mother's second pregnancy or a few weeks after the birth of the second child into the family. It can be supposed that in these cases the characteristic attitudes of the eldest child in the family had not developed prior to the onset of the disease.

Social stat of the family

In this study the social categories established by the Statistical Bureau for the City of Helsinki and for Espoo are used. They are based on the social esteem felt to be achieved by different vocations According to these categories Persons in professional and managerial positions belong to Group I. Persons directing small enterprises, foremen, higher office personnel, etc., belong to Group II. Skilled workmen lower office personnel, etc., belong to Group III and unskilled workmen to Group IV (56)

Table 11 shows the social grouping of the families in the GF and the P groups respectively

Table 11 Social groups.

	I	II	III	IV	Total
GF	1	4	20	5	30
P	2	10	16	2	30
	3	14	36	7	60

When in the statistical calculations Social Groups I and II were combined, and, similarly Social Groups III and IV it was discovered that the two upper social groups were more frequently found in the P category than in the GF category Accordingly the two lower social groups were more frequent in the GF category than in the P category The difference is statistically significant ($p < 0.05$)

In the following table the social grouping of the study material is compared with the social grouping of Helsinki City and Espoo, 1965 These are the only comparable data available, because only two communities in Finland, Helsinki and Espoo, have statistics on the social grouping of their inhabitants.

Table 12. Social grouping compared with the social grouping of Helsinki and Espoo

	I	II	III	IV	Unknown
Social groups in the study material	5 %	23.3 %	60 %	11.7 %	
Social groups in Helsinki	18.8 %	23.1 %	40.4 %	13.4 %	4.3 %
Social groups in Espoo	21.5 %	22.2 %	37.8 %	12.3 %	6.2 %

As can be seen from the above figures the greatest differences from the comparison populations are found in Social Groups I and III It can be supposed, however that in Helsinki and Espoo the incidence of professional and managerial positions is higher than in small communities. Further in the series the number of children of small farmers, belonging to group III, is rather high.

Heredity

Table 5 shows the occurrence of known cases of diabetes among the relatives of the children of the two groups

Table 5 Relatives with diabetes

	GF	P	Total
Diabetes in first degree relatives	8	14	22
Diabetes in more distant relatives	8	7	15
No known diabetic relatives	14	9	23
	30	30	60

The term first degree relatives in this study includes the patient's siblings parents grand parents and first cousins There is no statistically significant difference between the groups.

The series included six families in which *more than one child is affected with diabetes* Table 6 shows these cases distributed according to diabetic control.

Table 6 Diabetic control in siblings

Number of families	GF	P	Ungrouped	Total
6	3	7	3	13

These six families as is shown in Table 6 have altogether 13 diabetic children Of these 13 children 9 are included in the material.

Four are excluded for the following reasons In two cases the diabetes was of less than one year's duration in another case the child was so young that it was not possible to give her psychological tests used in this study and in the remaining case the patient was over fifteen years old at the time of the study

Growth

In the present investigation the data on height at the time of diagnosis of diabetes and at the time of the last examination have been obtained These figures have been compared with the normal values for Finnish children published by the Center for Study in Child Growth and Development (74) Table 7 shows the comparative heights at the time of diagnosis for the GF and the P groups respectively

Table 7 Height at the diagnosis of diabetes.

	GF	P	Total
Height above normal	3	—	3
normal	26	30	56
below normal	1	—	1
	30	30	60

Table 8 shows the heights of the two groups at the time of the last investigation.

Table 8 Height at the time of the last investigation

	GF	P	Total
Height above normal	—	—	—
normal	29	23	52
„ below normal	1	7	8
	30	30	60

The frequency of stunted growth at the time of the last examination in the series is 13.3 % (3.3 % in the GF group and 23.3 % in the P group)

The figures presented in Tables 7 and 8 are too small for statistical treatment. Moreover they cannot be considered as final figures, because the majority of the patients have not yet reached adult stature. There is however a tendency for the heights to be below the lower normal limit in the P group In the GF group there is only one child whose height at the time of the last investigation was below normal This is the same child whose height was already below the lower normal limit at the diagnosis of diabetes (Table 7) The growth retardation observed in the P group may thus in some way be connected with the control of the diabetes.

2 Social and socio psychiatric data

Size of the family

Table 9 shows the total number of children in the families of the GF and the P groups respectively

Table 9 Total number of children

Number of children	GF	P	Total
1 child	2	5	7
2 children	8	4	12
3 children	9	7	16
4 to 5 children	4	6	10
6 to 8 children	6	8	14
9 to 11 children	1	—	1
	30	30	60

Birth rank

Table 10 shows the birth rank of diabetic children in the GF and the P groups respectively

Table 10 Birth rank

	GF	P	Total
Only child	2	5	7
Youngest child	8	9	17
Eldest child	11	3	14
Middle child	9	13	22
	30	30	60

The children's emotional health before the onset of diabetes

Table 15 shows the incidence of neurotic and characterological symptoms in the children before the onset of diabetes.

Table 15. Neurotic and characterological symptoms in the children before the onset of diabetes.

	GF	P	Total
Enuresis	—	4	4
Encopresis	—	1	1
Enuresis and encopresis	1	—	1
Anxiety state, childhood phobias	—	1	1
Behavioral disturbances (defiance, hitting out at once)	1	—	1
	2	6	8

There ar considerable differences of opinion in the literature regarding the age t which a child should be labeled enuretic or encopretic. In this study the data obtained by Bellman in wedish population are used the ame limit for enuresis t 4 years nd for encopresi between 3 and 4 years (8)

Although the figures in T ble 15 are far too small for any conclusions t might be noted that in this series the children who later developed poor control of their diabetes had slightly higher incidence of enuresis at the time of onset of diabetes

Moreover it is a common observation that some of the more permanent personality disorders are easily overlooked or wrongly interpreted as transient by the parents This is especially true in the case of young children. Because of the significantly earlier age of onset in the P group a greater number of disturbed children belonging to that group may not hav been included in the figures.

Emotional stress as a precipitating factor

Table 16 shows the known incidence of different stressful life situation in the cases of the series.

Table 16. Types of stressful life situations

	GF	P	Total
Death of a relative	2	1	3
Starting school	1)	1	2
Birth of a sibling	3	1	4
Separation from home	—	1	1
Family move to another locality	—	1)	1
Physical injury intrinsically harmless, but shocking for the child	—	1)	1
Sibling seriously injured in traffic accident	—	1	1
	6	7	13

The cases marked) are those where the mother or the child spontaneously connected the event with the onset of the child's diabetes.

As is shown in Table 16 the incidence of tressful life situations prior to diagnosing the ch ld' diabetes is about the same in both diabetic groups

3 Th f m ly t t th h ld' ll

Imm diat action

By means of interviews with parents as well as by observing them during the visiting hours on the ward an attempt was made to learn how the parents reacted to the fact that the r child had diabetes For most of the parents the feeling was bewilderment and even shock, and many felt sad and depressed In the following the most typical responses of the parents are presented with the inner feelings which, in the author opinion, they reflected.

Bewilderment and shock As if everything had stopped. As if blank wall had risen in front of me "Everything was in confusion

Anxiety and fears. "I myself will be taken to mental hospital" "I am afraid of the insulin injection I fear the diet

Depressive feelings: "W were qu t down for a long time "W thought he might die in the hospital"

Guilt feelings both realistic and unrealistic, were found in connection with depressive feelings. They were conveyed in the following statements

Realistic guilt feelings Mother was working long hours outside of the home and did not have time to take the child to the doctor earlier.

Unrealistic guilt feelings. "The child was breast fed for more than 1½ years was it

Mother's employment

Of the 60 children included in the study the mothers of 46 worked solely at home. 25 of these 46 children belonged to the GF group and 21 to the P group. The mothers of another 5 children in the GF group and of 6 children in the P group held full time jobs away from home. In another 2 of the P group cases the mothers were working part time outside the home. In the last case the mother of the diabetically poorly controlled child is dead.

Table 13 shows the mother's employment for the GF and the P groups respectively.

Table 13. Mother's employment

	GF	P	Total
Housewife	25	21	46
Part time away from home	—	2	2
Full time away from home	5	6	11
Mother deceased	—	1	1
	30	30	60

The overall incidence of mothers working away from home is 22 % (16 % in the GF group and 28 % in the P group). These figures are relatively low when compared with the overall incidence of married women in gainful employment in Finland. Exact comparative data can be obtained only from the Statistical Bureau of the city of Helsinki where in 1965 56 % of married women were working away from home.

This difference can be partly explained by the fact that our Children's Hospital serves a large number of country communities as well as the city of Turku itself. A high proportion of the population in these communities are farmers. 14 of the diabetics in the series are the children of small farmers and the mothers take an active part in the farm work.

There are of course many other factors affecting the mother's decision on whether to remain at home or work away from home. One of them is that the opportunities for a woman to find a job within a reasonable distance from home are greater in cities and in industrial centers than in country communities.

Three of the mothers left their employment after the children developed diabetes. Two of the children belong to the GF group and one to the P group. The mothers of the children with Good or Fair Control have remained at home though one of them has seriously considered returning to work on two different occasi[...]. Each time the child developed ketoacidosis [...] had to be hospitalized. The mother in the [...] of Poor Control has returned to work a[...] from home.

Stability of the home

A study like this can reveal only the m[...] obvious cases of psychological disruption in [...] home. The reasons for this are twofold. 1) [...] number of interviews per family is small and [...] the study is essentially centered around the ch[...] and his illness. With these reservations in mi[...] the following results are presented.

All the children seem to have relatively sta[...] homes. All but one child have mother and fat[...] living at home. In that one case, belonging to [...] P group, the mother is dead. There is one ch[...] in each group whose mother has been previou[...] married.

Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's illness

Table 14 shows the incidence of emotio[...] disturbances and psychosomatic conditions in t[...] parents of the GF group and the P gro[...] respectively.

Table 14. Emotional disturbances and psych[...]somatic conditions in the parents before t[...] onset of the child's diabetes.

	GF	P	Tot[...]
Neurotic symptoms in the mother	2	3	5
Depressive state in the mother	1	—	1
Psychosomatic condition in the mother	—	1	1
Neurotic symptoms in the father	1	1	2
Depressive state in the father	1	1	2
Psychosomatic condition in the father	—	1	1
Psychotic episodes in both parents	1	—	1
No known emotional disturbances or psychosomatic conditions	24	23	47
	30	30	60

The incidence of emotional disturbances an[...] psychosomatic conditions in the parents is abou[...] the same in the two groups. 6 cases in the G[...] group and 7 cases in the P group. Of thes[...] 13 cases 3 have been hospitalized, 4 have been treated by private physicians and 6 have neve[...] sought professional help for their conditions.

The children's emotional health before the onset of diabetes

Table 15 shows the incidence of neurotic and characterological symptoms in the children before the onset of diabetes.

Table 15 Neurotic and characterological symptoms in the children before the onset of diabetes

	GF	P	Total
Enuresis	—	4	4
Encopresis	—	1	1
Enuresis and encopresis	1	—	1
Anxiety state childhood phobia	—	1	1
Behavioral disturbances (defiance, hitting out at once)	1	—	1
	2	6	8

There are considerable differences of opinion in the literature regarding the age at which a child should be labeled enuretic or encopretic. In this study the data obtained by Bellman in Swedish population are used, the age limit for enuresis at 4 years and for encopresis between 3 and 4 years. (8)

Although the figures in Tabl 15 are far too small for any conclusions it might be noted that in this series the children who later developed poor control of their diabetes had slightly higher incidence of enuresis at the time of onset of diabetes

Moreover it i a common observation tha some of the more permanent personality disorders are easily overlooked or wrongly terpreted as transient by the parents. This is especially true in the case of young children. Because of the significantly earlier age of onset in the P group a greater number of disturbed children belonging to that group may not have been included in the figures.

Emotional stress as a precipitating factor

Table 16 shows the known incidence of different stressful life situations in the cases of the series.

Table 16 Types of stressful life situations

	GF	P	Total
Death of a relative	2	1	3
Starting school	1)	1	2
Birth of a sibling	3	1	4
Separation from home	—	1	1
Family move to another locality	—	1)	1
Physical injury intrinsically harmless but shocking for the child	—	1)	1
Sibling seriously i jured in traffic accident	—	1	1
	6	7	13

The cases marked) are those where the mother or the child spontaneously connected the event with the onset of the child' diabetes

As is shown in Table 16, the incidence of stressful life situations prior to diagnosing the ch ld's diabetes is about the same in both diabetic groups.

---

3 Th f m ly a t o t th h ld' 1l

Immediat reaction

By means of interviews with parents as well as by observing them during the visiting hours on the ward an ttempt was made to learn how the parents reacted to the fact that the child had diabetes. For most of the parents the feeling was bewilderment and even shock, and many fel sad and depressed In the following the most typical responses of the parents are presented with the inner feelings which, in the author opinion, they reflected.

Bewilderment and shock As if everything had stopped. As if blank wall had risen in front of me "Everything w in confusion

Anxiety and fears "I myself will be taken to mental hospital" "I am afraid of the insulin injection "I fear the diet

Depressive feelings "We were quite down for long time" "W thought he might die in the hospital"

Guilt feelings both realistic and unrealistic, were found in connection with depressive feelings. They were conveyed in the following statements

Realistic guilt feelings. Mother was working long hours outside of the home and did not have time to take the child to the doctor earlier

Unrealistic guilt feelings: "The child was breast fed for more than 1½ years, was it

Mother's employment

Of the 60 children included in the study the mothers of 46 worked solely at home. 25 of these 46 children belonged to the GF group and 21 to the P group The mothers of another 5 children in the GF group and of 6 children in the P group held full time jobs away from home. In another 2 of the P group cases the mothers were working part time outside the home In the last case the mother of the diabetically poorly controlled child is dead

Table 13 shows the mother's employment for the GF and the P groups respectively

Table 13 Mother's employment

	GF	P	Total
Housewife	25	21	46
Part time away from home	—	2	2
Full-time away from home	5	6	11
Mother deceased	—	1	1
	30	30	60

The overall incidence of mothers working away from home is 22 % (16 % in the GF group and 28 % in the P group) These figures are relatively low when compared with the overall incidence of married women in gainful employment in Finland Exact comparative data can be obtained only from the Statistical Bureau of the city of Helsinki where in 1965 56 % of married women were working away from home.

This difference can be partly explained by the fact that our Children's Hospital serves a large number of country communities as well as the city of Turku itself A high proportion of the population in these communities are farmers 14 of the diabetics in the series are the children of small farmers and the mothers take an active part in the farm work

There are of course many other factors affecting the mother's decision on whether to remain at home or work away from home One of them is that the opportunities for a woman to find a job within a reasonable distance from home are greater in cities and in industrial centers than in country communities

Three of the mothers left their employment after the children developed diabetes Two of the children belong to the GF group and one to the P group The mothers of the children with Good or Fair Control have remained at home though one of them has seriously considered returning to work on two different occasions. Each time the child developed ketoacidosis and had to be hospitalized. The mother in the case of Poor Control has returned to work away from home.

Stability of the home

A study like this can reveal only the most obvious cases of psychological disruption in the home The reasons for this are twofold 1) the number of interviews per family is small and 2) the study is essentially centered around the child and his illness With these reservations in mind, the following results are presented

All the children seem to have relatively stable homes All but one child have mother and father living at home In that one case, belonging to the P group the mother is dead. There is one child in each group whose mother has been previously married.

Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's illness

Table 14 shows the incidence of emotional disturbances and psychosomatic conditions in the parents of the GF group and the P group respectively

Table 14 Emotional disturbances and psychosomatic conditions in the parents before the onset of the child's diabetes.

	GF	P	Total
Neurotic symptoms in the mother	2	3	5
Depressive state in the mother	1	—	1
Psychosomatic condition in the mother	—	1	1
Neurotic symptoms in the father	1	1	2
Depressive state in the father	1	1	2
Psychosomatic condition in the father	—	1	1
Psychotic episodes in both parents	1	—	1
No known emotional disturbances or psychosomatic conditions	24	23	47
	30	30	60

The incidence of emotional disturbances and psychosomatic conditions in the parents is about the same in the two groups 6 cases in the GF group and 7 cases in the P group Of these 13 cases 3 have been hospitalized 4 have been treated by private physicians and 6 have never sought professional help for their conditions

cases than is possible in a study like this. Two tentative interpretations are therefore offered.

1) In about two thirds (16 out of 24) of the mothers of children who later achieved well or fairly controlled diabetes, the initial insomnia subsided in less than 1 month.

It can be conjectured that the mothers of children in the GF group were able to work through and gain mastery over the initial anxiety and depression more quickly than the mothers of the P group children whose unresolved grief may have been the cause of more persistent insomnia.

2) If the defence mechanism of denial started to operate in the parents minds quickly after the child' illness was diagnosed, it is possible that the mothers, in denying the difficulties inherent in the situation, also have forgotten short-lived insomnias.

Development of coping devices

External coping devices

In the course of this study it could be seen how the parents, after the initial period of bewilderment, anxiety depression etc gradually started to adjust to the child's illness. The diabetic regimen became a part of the family's normal daily life. Many mothers expressed this by saying "When one gets to know the illness it becomes less frightening or "I realized that my child can lead an almost normal life or "It could be worse. Blind, deaf and crippled children are much worse off" In some instances the parents anxiety diminished when the child himself took part of the responsibility The adjustment to the child' illness takes place at two different levels the parents learn to handle the tasks of the child's illness and at the same time they become able to defend themselves against feelings of anxiety depression, etc. In other words the parents learn how to handle both the internal and external pressures to which they are exposed by the child' illness. To clarify the individual differences in these adjustment processes and the ways they affect the course of the child's illness are among the aims of the present study

I this study the terms external coping, coping process and coping device refer to the ways in which the parents handle the arious — usually daily — tasks caused by the child's illness. These devices can be grouped into two main categories.

1) *Constructive external coping devices* and
2) *Non-constructive external coping devices*

1) *Constructive external coping devices* The parents show a tolerant and responsible acceptance of the situation. In practical terms, this means that the parents seriously take into account the limitations and requirements imposed by the child's illness, while at the same time they emphasize the normal aspects of the child's life.

2) *Non-constructive coping devices* can be divided into the following subcategories

a) *Poor co-operation in dietary regimen* the parents fail to provide the child with an adequate diabetic diet (sugar free, low in carbohydrates and fat, rich in protein) because they do not really believe it necessary for the child.

b) *Poor co-operation in medical check-ups* the parents neglect the regular medical care of their diabetic child, failing to bring him for regular visits to the out-patient department.

c) *Helplessness about dietary regimen* becoming evident in three different ways.

— the child refuses to eat the prescribed diet and the mother accedes to this through passive resignation and freely giving the child unsuitable food, usually carbohydrate and fat,

— the child buys sweets with his pocket money every day on his way to or from school and the parents fail to, prevent it,

— often the school cook regularly "forgets" to prepare suitable food for the diabetic.

d) *Helplessness about insulin injections*: The parent is so insecure, helpless or phobic that he cannot give the insulin injections. There are only few helpless families in this regard in this series if one parent is unable to give the injections the other usually takes the responsibility There may be more helpless fathers than is indicated by the figures below If the mother is capable of handling this situation adequately the family is not rated as a helpless family

The parents may be helpless in more than one area of diabetic care; in these instances they are rated according to the area which seems to cause the greatest difficulty in the child daily care.

because of that he developed diabetes? "Father was sick with a heart condition at the time the child was conceived could this cause his diabetes? "Perhaps I gave him too many sweets. I was never given sweets in my childhood and I thought I would make it up to my children The guilt feelings are also clearly revealed in questions like "Why did it happen to us? What had I done to deserve this punishment?"

Aggression In some instances the child's illness apparently brought out aggressive feelings in the patent towards the child "It would be better if the child were to die than remain sick In other instances the aggressive feelings were directed towards the hospital personnel, who were accused and berated.

Wishful thinking In some instances the parents consoled themselves with wishful thinking, usually imagining that the diagnosis of diabetes was mistaken or that the diabetes could be totally cured Perhaps it is a mistake" It can only be a temporary upset" There must be some place in the world where diabetic children are treated without insulin "Do diabetics have a bracelet to indicate the level of the blood sugar?"

Table 17 lists the immediate reactions of the parents of children in the GF and P groups respectively It also shows the incidence of the immediate feelings and reactions of the parents

Table 17 Immediate reactions of parents

	GF	P
Bewilderment shock	17	16
Anxiety fears hysterical behavior phobic symptoms	21	22
Insomnia	24	11
Depressive feelings realistic and unrealistic guilt feelings	24	19
Aggression towards the child or the hospital personnel	1	1
Wishful thinking	7	1

Two mothers sought medical help for their own conditions during the initial stage of the child's illness

In the initial stages of the study the author was impressed by the fact that some of the very parents whose immediate behavior was most anxious fearful depressed and even disorganized had been able in the course of a few weeks po make an adequate adjustment, both externally and internally as it were, to the child's illness. As the study progressed and when all the data were gathered it became evident that those first few parents had not been exceptions. On the contrary as is shown in Table 17 the frequency of initial bewilderment or shock, anxiety fears, hysterical and phobic symptoms as well as depressive feelings was about the same in the parents of both groups. The differences were *mainly in the following areas*

1) *Initial insomnia* was about twice as common in the parents (usually mothers) of what later became the GF cases

2) *Wishful thinking* was also more common in the mothers of the GF group.

The overall picture of the immediate reactions is much more emotional vivid and colorful in the mothers of the GF group than in those of the P group

The reason for this can not be stated for certain. It can be hypothesized however that from the very beginning the parents of the P group have denied that strong emotions were aroused by the situation As will be pointed out later the defence mechanism of denial plays a prominent role in the later adjustment of parents of the P group to their child's illness.

Table 18 shows the duration of initial insomnia in parents of the subsequently GF and P cases respectively

Table 18 *Duration of insomnia*

	GF	P
Less than 1 week	10	1
1 week to 1 mo	6	2
1 mo to 6 mo	5	4
6 mos to 1 yr	1	—
More than 1 yr	2	4
	24	11

The figures are too small to be evaluated statistically Nevertheless from these figures one gains the impression that in the parents of the GF group the insomnia tended to subside more quickly than in the parents of the P group Again the reason for this is unknown and could be convincingly revealed only by a much more detailed scrutiny of individual

cases than is possible in a study like this. Two tentative interpretations are therefore offered

1) In about two thirds (16 out of 24) of the mothers of children who later achieved well or fairly controlled diabetes, the initial insomnia subsided in less than 1 month.

It can be conjectured that the mothers of children in the GF group were able to work through and gain mastery over the initial anxiety and depression more quickly than the mothers of the P group children whose unresolved grief may have been the cause of more persistent insomnia.

2) If the defence mechanism of denial started to operate in the parents minds quickly after the child' illness was diagnosed, it is possible that the mothers, in denying the difficulties inherent in the situation, also have forgotten short-lived insomnias

Development of oping devices

External coping devices.

In the course of this study it could be seen how the parents, after the initial period of bewilderment, anxiety depression etc., gradually started to adjust to the child' illness The diabetic regimen became a part of the family's normal daily life Many mothers expressed this by saying "When one gets to know the illness, t becomes less frightening or "I realized that my child can lead an almost normal life or It could be worse Blind, deaf and crippled children are much worse off" In some instances the parents anxiety diminished when the child himself took part of the responsibility The adjustment to the child illness takes place at tw different levels the parents learn to handle the tasks of the child's illness and t the same time they become able to defend themselves against feelings of anxiety depression, etc. In other words the parents learn how to handle both the internal and external pressures to which they are exposed by the child's illness. T clarify the individual differences in these adjustment processes and the way they affect the course of the child' illness are among the aims of the present study

I this study the terms external coping, coping process and coping device refer to the way in which the parents handle the various — usually daily — tasks caused by the child's illness. These devices can be grouped into two main categories

1) *Constructive external coping devices* and
2) *N n-constructive external coping devices*

1) *Constructive external coping devices* The parents show a tolerant and responsible acceptance of the situation. In practical terms, this means that the parents seriously take into account the limitations and requirements imposed by the child's illness, while at the same time they emphasize the normal aspects of the child's life.

2) *Non-constructive coping devices* can be divided into the following subcategories

a) *Poor co-operation in dietary regimen* the parents fail to provide the child with an adequate diabetic diet (sugar free, low in carbohydrates and fat, rich in protein) because they do not really believe it necessary for the child.

b) *Poor co-operation in medical check-ups.* the parents neglect the regular medical care of their diabetic child, failing to bring him for regular visits to the out-patient department.

c) *Helplessness about dietary regimen* becoming evident in three different ways.

— the child refuses to eat the prescribed diet and the mother accedes to this through passive resignation and freely giving the child unsuitable food, usually carbohydrate and fat

— the child buys sweets with his pocket money every day on his way to or from school and the parents fail to, prevent it,

— often the school cook regularly forgets to prepare suitable food for the diabetic.

d) *Helplessness about insulin injections* The parent is so insecure, helpless or phobic that he cannot give the insulin injections. There are only few helpless families in this regard in this series If one parent is unable to give the injections, the other usually takes the responsibility There may be more helpless fathers than is indicated by the figures below if the mother is capable of handling this situation adequately the family is not rated as a helpless family

The parents may be helpless in more than one area of diabetic care; in these instances they are rated according to the area which seems to cause the greatest difficulty in the child' daily care.

Table 19 shows the distribution of different external coping devices in the parents in the GF and P groups respectively

Table 19 *External coping devices*

	GF	P	Total
Constructive coping	25	5	30
Non-constructive coping	5	25	30
a) poor co-operation in dietary regimen	(2)	(13)	(15)
b) poor co-operation in medical check ups	(1)	(2)	(3)
c) helplessness about dietary regimen	(1)	(8)	(9)
d) helplessness about insulin injections	(1)	(2)	(3)
	30	30	60

As is shown in Table 19 the constructive coping devices were much more common in the GF group (25 cases) than in the P group (5 cases) On the other hand helplessness and poor co-operation were frequent findings in the P group (25 cases) as compared with the 5 cases in the GF group These differences are statistically significant ($p < 0.001$)

One of the main areas where the family's coping with the child's illness can be observed is the handling of the *diabetic dietary regimen* This is shown in Table 20

Table 20 *The child's diet*

	GF	P	Total
Sugar free low in carbohydrates and fat rich in protein	19	7	26
Excess in carbohydrates (bread and potatoes)			
daily or several times a week	3	4	7
once a week — once a month	1	—	1
Excess of fat			
daily or several times a week	1	3	4
once a week — once a month	—	1	1
Free diet without sugar	—	9	9
Deserts candies etc			
daily or several times a week	4	3	
once a week — once a month	2	1	3
No dietary restrictions	—	2	2
	30	30	60

Eleven families in the GF group have adopted the child's diet abandoning sugar and cutting down on fat In two other families where the other members of the family have no dietar restrictions the mother has given special attentio to the child's diet attending courses readin literature, etc. Such phenomena have no occurred in the families of the P group

The decision of the family to keep to a die which is suitable for their diabetic child require good co-operation from all the members of th family An example of this is a mother wh relates the following episode: "When I cam home, after our child's diabetes had bee confirmed my husband made the decision fo us all. He said that we were all going t follow the child's diet." This of course, require an empathetic relationship toward the sick child The following example may serve as an illustratio of an entirely different reaction to the child's diet: The mother of a poorly controlled child said that when she came home, after the child's diabetes had been diagnosed the father took th sugar bowl away from the coffee table th mother put it back on the table, insisting that it should remain there "By every means I have tried not to pay too much attention to the child's illness.

Daily insulin injections form another important area where the coping devices of the parents can be seen. Table 21 shows who is the person giving the insulin injections in the families of the GF and the P groups respectively

Table 21 *Person(s) who give the daily insulin injections*

	GF	P	Total
Mother	14	17	31
Father	2	6	8
Mother and child in turn	11	3	14
Father and child in turn	—	2	2
Mother and father in turn	3	2	5
	30	30	60

There are 16 families in the GF group in which only one member either mother or father gives the daily insulin injections as compared with 23 such families in the P group Further there are twice as many families (14) in the GF group where the members take turns in giving the daily insulin injections a compared with 7 families in the P group The difference statistically almost significant ($p < 0.10$) The most probable explanation for this is that in the GF group the members of the family experience diabetic care as a common responsibility

Internal coping devices

In this study the terms internal coping, internal coping process and internal coping device refer to the various maneuvers which the parents use to avoid the feelings of anxiety Internal coping is a silent one (= unconscious) operation but manifests itself in the person s words and actions. Of many possible coping devices, each individual tends to rely on few which then become characteristic for him.

The following internal coping devices were observed operating in the parents of the cases under study·

1) Many parents were able to admit to feelings of anxiety loss and depression and at the same time were able to control them adequately In many instances the parents find some enjoyment in caring for the sick child In way they have channeled their anxiety into socially valuable and rewarding behavior This coping device comes close to the concept of sublimation which in earlier psychoanalytic writings has been viewed as one of the mature defence mechanisms

On the other hand, Kubie has shown how the concept of sublimation in the hands of various authors has implied many different things, no two authors being consistent For this reason among others Kubie recommends that the concept be discarded (84)

2) Some parents were apparently unable to admit the painful feelings aroused by their child s illness They tended to deny them. Both external events and internal feelings can be denied. The denial of external events implicitly means that the internal pain is also denied

A few examples of parents statements might be quoted "I have no sick child" "The doctor told me tha my child is serious case but I cannot regard him as such A cold the head is orse than diabetes

3) In some cases the denial of feeling of helplessness apparently leads to an omnipotent attitude regarding the care of the diabetic child The parents usually the mother think that they know everything about the diabetic regimen, more than the medical personnel The rationalization behind this is their feeling that because they have taken care of the diabetic child 4 hours day for so many years, they must know mor about the disease than those whose knowledge is based on books and short term care of the child n the hospital "Of course, the doctor knowledge doesn t do me any harm one of the mothers remarked In simpler form, the omnipotent attitude comes out in a statement like th following (by a mother of a poorly controlled child) "My child is the best treated diabetic in the whole vicinity Omnipotent thinking closely resembles the defence mechanism which is known as reaction formation. This is a mechanism whereby one of a pair of ambivalent ttitudes (e.g. helplessness and omnipotence) is repressed and kept unconscious by overemphasis on the other Finch and Hess who observed the parents of 17 children with ulcerative colitis, reached conclusions very similar to those described above. They reported that in all their cases the mother appeared dominating and over-controlling toward the patient. The mothers consciously demonstrated extreme though superficial, concern for the child, but in many cases the mother's negative ttitude was shown in her apparent need for illness in the child (43)

4) Some parents had feelings of being permanently helpless, impotent, and resigned in the face of the painful situation caused by the child s illness. In this study the term depression is used to describe this kind of affective response according to Sandler and Joffe description

Its core is a basic depressive-affective response, but it includes as well a number of features which may be understood as representing attempts to deal with the existence of this affect or directed towards preventing its emergence. In particular because of the important role which undischarged aggression plays in the genesis of the depressive response, we find derivatives of or defences against, aggressive manifestations also complicating the picture The depressive reaction, considered as basic affective state, may like anxiety be of long or short duration, of low or high intensity and it can occur in a wide variety of personality types and clinical conditions. It can occur at any developmental stage and is found in association with obsessions phobias, etc. (116)

5) The experiencing of mental pain normally mobilizes aggression which is then directed against what is felt to be the source of the pain. There are several cases in the series where the parent s aggression apparently was felt against the sick child. This can be exemplified by a statement of a mother· I once read in a newspaper about mother who had hidden her child in a closet for many years My friends were horrified when the read it, but I can understand that mother I find it difficult to walk on the treets with my short child

In other instances the aggression was directed toward the hospital personnel the school authorities etc. The defence mechanism called displacement apparently operates in the parents minds in these latter instances This is a defence mechanism which shifts the goal of the danger of the alarming impulse by attributing the affect (in this case aggression) to some other cause

6) In phobias the person s own frightening impulses are first projected and then displaced onto an external event. A few of the parents in this study apparently used this defence mechanism to master their anxiety The resulting phobia usually involved insulin injections

Interrelationship between external and internal coping devices

Table 22 shows the interrelationships between various external and internal coping devices in the GF group and Table 23 in the P group respectively

Table 22 *External and internal coping devices in the GF group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	18	2		4	1		25
Poor co-op in dietary regimen		2					2
Poor co-op in med check-ups					1		1
Helplessness in dietary regimen	1						1
Helplessness in ins.inj						1	1
	19	4		4	2	1	30

Table 23 *External and internal coping devices in the P group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	3	1		1			
Poor co-op in dietary regimen		6	4	2	1		13
Poor co-op in med. check ups		1		1			
Helplessness in dietary regimen		2		5	1		8
Helplessness in ins. inj		1		1			[illegible]
	3	11	4	10	2		30

As can be seen from the above tables the parent s ability to cope with the demands made upon them by their child s illness is very closely related to their ability to face and realistically work through the inner feelings of anxiety loss and depression which they experience in the first stages of the child s illness

The ability to face the feelings of anxiety etc and at the same time control them adequately is a much more common finding in constructive external coping than in non-constructive coping. On the contrary denial omnipotent thinking and persistent depression are more often related to the non-constructive external coping

4 The childs a tion to the diab tes

Immedial reactions

The child' immediate reaction to the discovery of diabetes in himself could be evaluated only in those cases where the child's first hospitalization occurred at the time the study took place There were 17 such cases among the *series of 60 In additional 3 cases* either the mother or the hospital record provided sufficient data for making an evaluation.

The immediate reactions are shown in Table 24

Table 24 The immedial reaction in children

Type of reaction	GF	P	Total
Anxiety reactions	10		10
H sterical paraly s	1		1
Depressive reaction	4		4
Smiling depression		1	1
Suicidal threats		1	1
Aggression towards the illness or the mother	2		2
No disturbances	1		1
	18		20

The figure in Table 24 are too small for det iled comparison In addition to this one has bear in mind that the child's reaction t the illness in many instances cannot be distinguished from his reaction to the hospitalization I a number of clinical and experimental studies on the emotional implications of hospitalization the main foci of anxiety have been *found to be*

) separation from the parents and exposure to the unfamiliar hospital surroundings and

b) fear of diagnostic and treatment procedures. Age was an important determinant of which ou d be more difficult for the child Anxiety about hospitalization and separation was greatest *in the youngest children (72, 109)*

Something can, however be said about the f gures in Table 24

1 the severity of the child's imm diate reaction especially the amount of anxiety displayed, does not seem to be related to the later controllability of his diabetes E en the very seriously disturbed child, the girl w th hysterical paralysis recovered emotionally in the course of a few weeks, and, at least during the subsequent three years has been a well controlled diabetic.

b) The term "Smiling depression was introduced by Toolan in the following words. "Boys especially have a need to hide their true feelings, particularly any soft tender weak sentiments. At times a *teenager may* deliberatly mask his true feelings by a pretence of happiness and exhibit the picture of smiling depression. (142) Figures 6 and 7 (page 34) illustrate this a patient in this series, a boy of 13 made a drawing while on the ward (*Figure 6*) and another drawing (Figure 7) on the same day at the psychiatric interview The drawing made on the ward is an artificially gay one while the drawing made during the psychiatric interview is rather sad and empty This particular instance came to the author's notice because the boy's first hospitalization took place during the collection of this study material. It can be hypothesized that this kind of reaction may be more common than is realized but difficult to trace because of the pretence of happiness.

Later adjustm ent

The psychiatric assessment of the child at the final stage of the study was based on three main sources of information.

1) data from interviews with the parents

2) the author's evaluation of the child, based on interviews or play observations

3) the teacher evaluation of the child s social adjustment at school.

If the child was hospitalized at the time this study took place the occupational therapist s weekly reports, as well as the observations of the ward personnel have also been used as additional sources of information.

Table 25 shows the list of symptomatic reactions displayed by the children in the GF and P groups respectively The reactions have been *grouped into* five main categories and several subcategories.

In other instances the aggression was directed toward the hospital personnel the school authorities etc. The defence mechanism called displacement apparently operates in the parents minds in these latter instances. This is a defence mechanism which shifts the goal of the danger of the alarming impulse by attributing the affect (in this case, aggression) to some other cause

6) In phobias the person's own frightening impulses are first projected and then displaced onto an external event. A few of the parents in this study apparently used this defence mechanism to master their anxiety The resulting phobia usually involved insulin injections

Interrelationship between external and internal coping devices

Table 22 shows the interrelationships between various external and internal coping devices in the GF group and Table 23 in the P group respectively

Table 22 *External and internal coping devices in the GF group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	18	2		4	1		25
Poor co-op in dietary regimen		2					2
Poor co-op in med. check ups					1		1
Helplessness in dietary regimen	1						1
Helplessness in ins.inj						1	1
	19	4		4	2	1	30

Table 23 *External and internal coping devices in the P group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	3	1		1			
Poor co-op in dietary regimen		6	4	2	1		13
Poor co-op in med check-ups		1		1			
Helplessness in dietary regimen		2		5	1		8
Helplessness in ins inj		1		1			2
	3	11	4	10	2		30

As can be seen from the above tables the parent's ability to cope with the demands made upon them by their child's illness is very closely related to their ability to face and realistically work through the inner feelings of anxiety loss and depression which they experience in the first stages of the child's illness.

The ability to face the feelings of anxiety etc and at the same time control them adequately is a much more common finding in constructive external coping than in non-constructive coping On the contrary denial omnipotent thinking and persistent depression are more often related to the non-constructive external coping

4 The hild's ction to th diabetes

mmediate reactions

The child's immediate reaction to the discovery of diabetes in himself could be evaluated only in those cases where the child first hospitalization occurred at the time the study took place. There were 17 such cases among the series of 60 I additional 3 cases either the mother or the hospital record provided sufficient d ta for making an evaluation.

The immediate reactions are shown in Table 24

Table 24 *The immediat reactions in childr n*

Type of reaction	GF	P	Total
Anxiety reactions	10		10
Hysterical paralysis	1		1
Depressive reaction	4		4
"Smiling depression		1	1
Suicidal threats		1	1
Aggression towards the illness or the mother	2		2
No disturbances	1		1
	18	2	20

The figures in Table 24 are too small for det iled comparison In addition to this, one has to bea in mind that the child' reaction t the illness in many instances cannot be distinguished from his reaction to the hospitalization In number of clinical and experimental tudies on the emotional implications of hospitalization the main foci of anxiety have been found to be

) separation from the parents and exposure to he unfamiliar hospital surroundings, and

b) fear of diagnostic and treatment procedures Age was an important determinant of which ou'ld be more difficult for the child. Anxiety about hospitalization and separation was greatest the youngest children (72, 109)

Some.hing can, however be said about the figures m Table 24

1 the severity of the child' mmediate reaction especially the amount of anxiety displayed does not seem t be related to th later controllability of his diabetes E en the very seriously disturbed child, the girl with hysterical paralysis recovered emotionally in the course of a few weeks and, at least during the subsequent three years, has been a well controlled diabetic.

b) The term "Smiling depression was introduced by Toolan in the following words "Boys especially have need to hide their true feelings, particularly any soft, tender weak sentiments. At times a teenager may deliberatly mask his true feelings by a pretence of happiness and exhibit the picture of a smiling depression." (142) Figures 6 and 7 (page 54) illustrate this a patient in this series a boy of 13 made a drawing while on the ward (Figure 6) and another drawing (Figure 7) on the same day at the psychiatric interview The drawing made on the ward is an artificially gay one while the drawing made during the psychiatric interview is rather sad and empty This particular instance came to the author's notice because the boy's first hospitalization took place during the collection of this study material. It can be hypothesized that this kind of reaction may be more common than is realized but difficult to trace because of the pretence of happiness.

Later adjustment

The psychiatric assessment of the child at the final tage of the study was based on three main sources of information

1) data from interviews with the parents

2) the author's evaluation of the child, based on interviews or play observations

3) the teacher's evaluation of the child's social adjustment at school.

If the child was hospitalized t the time this study took place, the occupational therapist's weekly reports, as well as the observations of the ward personnel, have also been used as additional sources of information.

Table 25 shows the list of symptomatic reactions displayed by the children in the GF and P groups respectively The reactions have been grouped into five main categories and several subcategories

In other instances the aggression was directed toward the hospital personnel the school authorities etc. The defence mechanism called displacement apparently operates in the parents minds in these latter instances. This is a defence mechanism which shifts the goal of the danger or the alarming impulse by attributing the affect (in this case aggression) to some other cause.

6) In phobias the person's own frightening impulses are first projected and then displaced onto an external event. A few of the parents in this study apparently used this defence mechanism to master their anxiety The resulting phobia usually involved insulin injections.

Interrelationship between external and internal coping devices

Table 22 shows the interrelationships between various external and internal coping devices in the GF group and Table 23 in the P group respecvtively

Table 22 *External and internal coping devices in the GF group*

	Admitting anxiety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	18	2		4	1		25
Poor co-op in dietary regimen		2					2
Poor co-op in med. check ups					1		1
Helplessness in dietary regimen	1						1
Helplessness in ins.inj						1	1
	19	4		4	2	1	30

Table 23 *External and internal coping devices in the P group*

	Admtting an.iety & depr but capable of adequate internal control	Denial	Omnipotent thinking	Depr	Aggr	Phobia	Total
Constructive coping	3	1		1			[illegible]
Poor co-op in dietary regimen		6	4	2	1		13
Poor co-op in med check-ups		1		1			
Helplessness in dietary regimen		2		5	1		8
Helplessness in ins inj		1		1			2
	3	11	4	10	2		30

As can be seen from the above tables the parent's ability to cope with the demands made upon them by their child's illness is very closely related to their ability to face and realistically work through the inner feelings of anxiety loss and depression which they experience in the first stages of the child's illness.

The ability to face the feelings of anxiety etc and at the same time control them adequately is a much more common finding in constructive external coping than in non-constructive coping. On the contrary denial omnipotent thinking and persistent depression are more often related to the non-constructive external coping.

4 The child was rated as having *a personality trait disorder* if the behavioral difficulties had become fixated patterns which the child carried over into all situations. In contrast to psychoneurosis, the personality trait disorders are more pervasive; there is not even the marginal healthy living a psychoneurotic child can have.

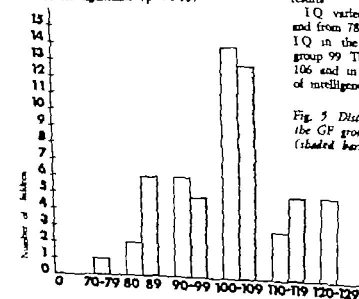
Table 26 shows the distribution of the abovementioned psychiatric diagnostic categories in the GF and the P groups respectively

Table 26 *Psychiatric diagnostic categories*

Diagnosis	GF	P	Total
Normal adjustment	11	4	15
Mild adjustment disorder	8	8	16
Psychoneurosis	8	4	12
Personality trait disorder	3	14	17
	30	30	60

As can be seen from Table 26 in the categories of normal adjustment and psychoneurosis the GF cases outnumber the P cases, whereas the personality trait disorders, in other words the more difficult emotional disturbances, are more frequent in the P group than in the GF group

When, in the statistical evaluation, normal adjustment and mild adjustment disorder were combined, and, similarly psychoneurosis and personality trait disorder it was discovered that normal adjustment and mild adjustment disorder were more frequent in the GF group than in the P group Accordingly psychoneurosis and personality trait disorder were more frequently found in the P group The difference is statistically almost significant ($p < 0.10$)



School achievement

The child's school achievement is based upon the teacher's evaluation. The teacher was asked to rate the child achievement as above average average or below average as compared with the average achievement of the class. The results are shown in Table 27

Table 27 *School achievement*

	GF	P	Total
Above average	11	5	16
Average	9	10	19
Below average	4	10	14
	24	25	49

The remaining 11 children have either left school or not yet entered school.

6 children in the P group have had to repeat class one of them twice. None of those in the GF group has repeated a class. As can be seen from Table 27 one third of the P cases are at the bottom of the academic achievement scale, while one third of the GF cases are at top of the academic achievement scale. The difference *is statistically almost significant* ($p < 0.10$)

5 Psychological data

The intelligence test

The T-M L intelligence test was given to all diabetic children in the study with the following results

I Q varied from 82 to 127 in the GF group and from 78 to 119 in the P group The average I Q in the GF group was 102 and in the P group 99 The median I Q in the GF group was 106 and in the P group 100 The distribution of intelligence quotients is shown in Fig 5

Fig. 5 Distribution of intelligence quotients in the GF group (white bars) and in the P group (shaded bars)

Table 25 *List of symptomatic reactions*

	GF	P	Total
A Disturbances related to Bodily Functions			
1 Sleeping			
Difficulty in falling asleep	2	1	3
Restless sleep	1	4	5
Night fears	1		1
2 Bladder Function			
Enuresis (nocturnal)	5	8	13
3 Speech and language			
Elective mutism		2	2
Infantile speech		1	1
Stuttering		1	1
4 Motor Patterns			
Hyperactivity	1	3	4
Passivity	1		1
Tics	1		1
B Developmental Difficulties			
1 Excessive separation anxiety		1	1
2 Problems in sexual identification		1	1
C. Disturbances in Social Behavior			
1 Aggressive Behavior	1	3	4
2 Antisocial Behavior			
Stealing		1	1
Lying		2	2
3 Oppositional Behavior			
Passive resistance		9	9
Passive-aggressive behavior		1	1
Disobedience		1	1
Running away		1	1
4 Isolated Behavior			
Withdrawal	2	4	6
Autistic behavior		1	1
5 Problems in Dependency — Independency			1
Clinging behavior	1		1
D Disturbances in Affective Behavior			
1 Manifest anxiety			
Anxiety attacks	3	5	8
Free floating anxiety	7	1	8
Uncontrollable crying screaming	2	4	6
2 Manifestly Fearful Behavior			
Specific fears	5	1	6
3 Manifest Depression			
Depressive episodes	1	1	2
Chronic depression		3	3
Feelings of inadequacy inferiority	4	5	9
E. Difficulties in Integrative Behavior			
1 Impulsive Behavior	1	2	3
2 Limited Tolerance of Frustration	1	1	2
3 Over use of Adaptive Mechanisms			
Over strenuous denial		1	1
Marked projection	1	1	2
Over-concern with cleanliness		1	1
Obsessive rumination		1	1
	41	72	113

Number of symptomatic reactions

In this study the children in the P group had more symptomatic reactions than the children in the GF group The number of symptomatic reactions per child was 1 3 in the GF group and 2 4 in the P group

Quality of symptomatic reactions

When, in statistical analysis the Disturbances related to Bodily Functions, Developmental Difficulties and Disturbances in Social Behavior were combined and, correspondingly Disturbances in Affective Behavior and Difficulties in Integrative Behavior were combined, it was found that the differences between the GF and P groups were mainly in the areas of Bodily Functions Personality Development and Social Behavior the children in the P group having a significantly greater number of disturbances. ($p<0.02$)

Difficulties in Affective and Integrative Behavior were equally frequent in the two groups

When finally the child's adjustment was evaluated the following criteria were used

1 The child was rated as having made *a normal adjustment* if he displayed none of the symptoms listed above and if all three sources of information indicated age-appropriate behavior

2 The child was rated as having *a mild adjustment disorder* if one of the three main sources of information, parents school or the examination indicated disturbed behavior in the form of the symptomatic reactions listed above.

3 The child was rated as having *a psychoneurosis* if at least two of the sources of information indicated signs of anxiety or depression or if the child had clear-cut phobic or hysterical symptoms

There is no statistically significant difference between the two diabetic groups
Impunitiveness
GF = 24.8 %
= 24.4 %
t = 0.033
p > 0.10

The difference between the two diabetic groups in terms of their Impunitiveness is even smaller than of their Extrapunitiveness or Intropunitiveness. The children in the two diabetic groups show equal tendencies to avoid and hide their aggressions evenly

Reaction Types

Obstacle Dominance
GF = 26.4 %
P = 28.3 %
t = 0.156
p > 0.10

Again the difference is so small that t has no statistical significance
Ego-defensive
GF = 31.8 %
P = 29.8 %
t = 0.122
p > 0.10

The difference is not statistically significant
Need persistence
GF = 23.5 %
P = 22.6 %
t = 0.078
p > 0.10

The difference between the two groups in terms of Need-Persistence variable is even smaller than in other instances

A summary of esponses to the Rosenzweig Picture Frustr on Test I can be said that no tatistically sign ficant differences could be observ ed betwe the hildren n the two diabetic group

The esult of the comparison between the diabeti children and normal control subjects

As is ndicated abo the normative data were obtained mainly from Rosenzweig's study of 256 children from 4 to 13 years of age and on Takala study of Finnish children

The results for each diabetic group are compared with Rosenzweig data

Directions of Aggression

Extrapunitiveness
GF = 58.4 % t = 1.041 p > 0.10
P = 56.8 % t = 0.746 p > 0.10
Normal group = 48.2 %

The children in each diabetic group give more overtly aggressive responses to the Rosenzweig P F Study The difference between the GF group and the Normal group is greater than between the P group and the Normal group. However the differences are not statistically significant. The above mentioned differences may be partly due to cultural features. Takala has found that the number of Extrapunitive responses of Finnish children exceed the Rosenzweig norms by 10 % in each age group When this is taken into account, the figures would be as follows
GF = 58.4 %
P = 56.8 %
Normal group
(Finnish
Children) = 58.2 %

Thus the GF group would come closer to the Normal group of Finnish children than the P group would do.

I tropunitiveness
GF = 16.8 % t = 0.973 p > 0.10
P = 18.8 % t = 0.654 p > 0.10
Normal group = 24.1 %

The children in each diabetic group give fewer responses, *indicating that they turn aggression* on themselves than the children in the Normal group do. The difference between the GF group and the Normal group is greater than between the P group and the Normal group Even the greater *difference is not statistically significant.*

Impunitiveness
the GF group = 24.8 % t = 0.081 p > 0.10
the P group = 24.4 % t = 0.119 p > 0.10
Normal group = 25.5 %

The children in each diabetic group give only slightly fewer responses to the Rosenzweig P-F Study that do not blame anyone. The differences are far from having statistical significance

The results broken down into three levels of intelligence are shown in Table 28

Table 28 Level of intelligence in the GF group and in the P group

I Q	GF	P	Total
Over 115 (above normal)	6	2	8
85 — 115 (normal)	23	23	46
Under 85 (below normal)	1	4	5
No result		1	1
	30	30	60

As can be seen from Table 28 one child in the P group is without result in the intelligence test This is a girl of 12 who refused to participate in the psychological testing

Statistical analysis shows that there is no significant difference in the intelligence between the children in the GF and the P group

Tb Rosenzweig Picture Frustration Test

The Rosenzweig Picture Frustration Test children s form consists of a booklet containing 24 cartoon-like drawings. In each drawing is a person either frustrating a child or insistently pointing out improper behavior on the part of a child The remarks of the frustrator are indicated whereas the child s responses are not given The child is requested to tell what he feels would be an appropriate answer

The responses for each test situation were analyzed in terms of the direction of aggression and of *types of reaction* to frustration. Each of these categories included three variables The response categories are presented in Table 29

Table 29 *Rosenzweig Picture-Frustration Test Variables*

Directions of Aggression	E Extrapunitiveness	Child turns aggression onto the environment
	I Intropunitiveness	Child turns aggression onto himself blames or accuses himself He willingly accepts blame and appears apologetic
	M Impunitiveness	Aggression is glossed over and evaded. Aggression does not appear in the response
Reaction Types	OD Obstacle-dominance	The frustrating barrier is out standing in the respons
	ED Ego-defensive	Personalities of the actors especially the frustrated child, dominate the response
	NP Need-persistence	Solution of frustrating problem is emphasized in the responses

The two diabetic groups (the GF group and the P group) were compared on the basis of the scores on each variable In addition to this the diabetic groups were compared with normative data reported by Rosenzweig and Takala (115 137)

One child in the GF group and three children in the P group refused to co-operate in the Rosenzweig Picture Frustration test Thus 29 test protocols were obtained from the GF group and 27 from the P group

The result of the comparison between the two diabetic groups

Directions of Aggression

Extrapunitiveness

GF $= 58.4$ %
P $= 56.8$ %
$t = 0.118$
$p > 0.10$

There is no statistically significant difference between the two diabetic groups

Intropunitiveness

GF $= 16.8$ %
P $= 18.8$ %
$t = 0.033$
$p > 0.10$

There is no statistically significant differenc between the two diabetic groups.

Impunitiveness

GF	= 24.8 %
	= 24.4 %
t	= 0.033
p	> 0.10

The difference between the two diabetic groups in terms of their Impunitiveness is even smaller than of their Extrapunitiveness or Intropunitiveness. The children in the two diabetic groups show equal tendencies to avoid and hide thei aggressions evenly

Reaction Types.

Obstacle-Dominance

GF	= 26.4 %
P	= 28.3 %
t	= 0.156
p	> 0.10

Again the difference is so small that it has no statistical significance

Ego defensive

GF	= 31.8 %
P	= 29.8 %
t	= 0.122
p	> 0.10

The difference is not statistically significant.

Need-persistence

GF	= 23.5 %
P	= 22.6 %
t	= 0.078
p	> 0.10

The difference between the two groups in terms of Need-Persistence variable is even smaller than n other nstances

A summary of responses to the Rosenzweig Picture Frustration Test t can be said that no statistically significant differences could be observed between the children in the two diabetic group

The sult of the comparison between the diabetic children and normal control subjects

As indicated abo the normative data ere obtained mainly from Rosenzweig tudy of 256 children from 4 to 13 years of age and on Takala study of Finnish children

The results for each diabetic group are compared with Rosenzweig s data

Directions of Aggression

Extrapunitiveness.

GF	= 58.4 %	t = 1.041	p > 0.10
P	= 56.8 %	t = 0.746	p > 0.10
Normal group	= 48.2 %		

The children in each diabetic group give more overtly aggressive responses to the Rosenzweig P-F Study The difference between the GF group and the Normal group is greater than between the P group and the Normal group However the differences are not statistically significant. The above mentioned differences may be partly due to cultural features. T kala has found that the number of Extrapunitive responses of Finnish children exceed the Rosenzweig norms by 10 % in each age group When this is taken int account ,the figures would be as follows

GF	= 58.4 %
P	= 56.8 %
Normal group (Finnish Children)	= 58.2 %

Thus, the GF group would come closer to the Normal group of Finnish children than the P group would do

Intropunitiveness

GF	= 16.8 %	t = 0.973	p > 0.10
P	= 18.8 %	t = 0.654	p > 0.10
Normal group	= 24.1 %		

The children in each diabetic group give fewer responses indicating that they turn aggression on themselves than the children in the Normal group do The difference between the GF group and the Normal group is greater than between the P group and the Normal group. Even the greater difference is not statistically significant.

Impunitiveness.

the GF group	= 24.8 %	t = 0.081	p > 0.10
the P group	= 24.4 %	t = 0.119	p > 0.10
Normal group	= 25.5 %		

The children in each diabetic group give only slightly fewer responses to the Rosenzweig P-F Study that do not blame anyone. The differences are far from having statistical significance.

The results broken down into three levels of intelligence are shown in Table 28

Table 28 Level of intelligence in the GF group and in the P group

I Q	GF	P	Total
Over 115 (above normal)	6	2	8
85 — 115 (normal)	23	23	46
Under 85 (below normal)	1	4	5
No result		1	1
	30	30	60

As can be seen from Table 28 one child in the P group is without result in the intelligence test. This is a girl of 12 who refused to participate in the psychological testing.

Statistical analysis shows that there is no significant difference in the intelligence between the children in the GF and the P groups

Tb Rosenzweig Picture Frustration Test

The Rosenzweig Picture Frustration Test children's form consists of a booklet containing 24 cartoon-like drawings In each drawing is a person either frustrating a child or insistently pointing out improper behavior on the part of a child The remarks of the frustrator are indicated whereas the child's responses are not given. The child is requested to tell what he feels would be an appropriate answer

The responses for each test situation were analyzed in terms of the direction of aggression and of types of reaction to frustration. Each of these categories included three variables. The response categories are presented in Table 29

Table 29 *Rosenzweig Picture-Frustration Test Variables*

Directions of Aggression	E Extrapunitiveness	Child turns aggression onto the environment
	I Intropunitiveness	Child turns aggression onto himself blames or accuses himself He willingly accepts blame and appears apologetic
	M Impunitiveness	Aggression is glossed over and evaded Aggression does not appear in the response
Reaction Types	OD Obstacle-dominance	The frustrating barrier is outstanding in the respons
	ED Ego-defensive	Personalities of the actors especially the frustrated child dominate the response
	NP Need persistence	Solution of frustrating problem is emphasized in the responses

The two diabetic groups (the GF group and the P group) were compared on the basis of the scores on each variable. In addition to this the diabetic groups were compared with normative data reported by Rosenzweig and Takala (115 137)

One child in the GF group and three children in the P group refused to co-operate in the Rosenzweig Picture Frustration test Thus 29 test protocols were obtained from the CF group and 27 from the P group

The results of the comparison between the two diabetic groups

Directions of Aggression

Extrapunitiveness

GF $= 58.4\ \%$
P $= 56.8\ \%$
$t = 0.118$
$p > 0.10$

There is no statistically significant difference between the two diabetic groups

Intropunitiveness

CF $= 16.8\ \%$
P $= 18.8\ \%$
$t = 0.033$
$p > 0.10$

20.	0.30961	
21.	0.30111	
22.	0.29910	
23	0.29825	
24	0.29488	
25	0.28988	
26	0.28431	
27	0.28331	
28.	0.25368	
29	0.25013	
30	0.13642	P
31	0.12155	
32.	0.11979	
33	0.08603	
34	0.08312	
35	0.07488	
36	0.07327	
37	0.07305	GF
38	0.07305	P
39	0.07305	
40	0.07305	
41	0.07305	
42	0.06020	
43	0.06020	
44	0.05470	
45	0.04524	
46	0.02884	
47	0.02688	
48	0.02477	
49	0.02441	
50	0.01645	
51	—0.01045	
52	—0.02332	
53	—0.02865	
54	—0.03266	
55	—0.04326	
56	—0.05741	
57	—0.06896	
58	—0.11030	
59	—0.12079	
60	—0.13400	

As can be seen from Table 31 the two diabetic groups differ clearly from each other on the Discriminant Line. There is only one exception, child belonging clinically to the GF group whose Discrimination Points locate him in the middle of the P group

Table 32 shows the Discriminant Function Coefficients obtained arranged in numerical order.

Table 32. *Discriminant Function Coefficients.*

1	Integration	0.0340
2.	Popular	—0.02489
3	Movement	—0.01914
4	Animal	0.01557
5	Color	0.01413
6.	Shading	0.01289
7	Barrier	—0.01050
8.	Hostility	—0.01006
9	Space	0.00910
10	Penetration	0.00875
11	Anatomy	0.00817
12.	Form Appropriateness	—0.00681
13	Human	—0.00590
14	Reaction Time	—0.00386
15	Pathogonomonic Verbalization	0.00325
16.	Rejection	0.00282
17	Form Definiteness	0.00152
18	Anxiety	—0.00075
19	Location	0.00034

Three variables, Abstraction, Sex and Balance, are not included in Table 32, because of the infrequency of responses obtained. The greater the absolute value of the discrimination function coefficient of any variable, the more important the variable will be in discriminating between the GF and the P groups. In this material those best discriminative variables are *Integration Popular Movement Animal Color Shading, Barrier and Hostility*

From these variables Movement Integration, Popular Barrier and Hostility have proved in number of factor-analytic studies to define the Holtzman Factor I which usually accounts for most of the variance. In the same manner the variables Color and Shading define the Factor II. (68) Consequently in this study the best discriminators between the two diabetic groups are the combinations of variables contributing to the Holtzman Factors I and II.

According to the interpretation of the factors, the major dimensions measured by these eight variables are as follows.

Factor I Perceptual Maturity and Integrated Ideational Activity

Invariably defined by Movement, Integration, Human, Barrier and Popular Factor I usually

Reaction Types

Obstacle-dominance

GF	= 26 4 %	t = 1 150	p > 0 10
P	= 28.3 %	t = 1.297	p > 0 10
Normal group	= 16.5		

The children in each diabetic group give more frustration-oriented responses to the Rosenzweig P E Study than the children in the Normal group do The difference between the GF group and the Normal groups is smaller than between the P group and the Normal group The differences are not statistically significant

Ego defensive

GF	= 31.3 %	t = 2 740	p < 0 01
P	= 29.8 %	t = 2.842	p < 0.01
Normal group	= 56.8 %		

The personalities of the actors especially the frustrated child dominate the responses of the children in the Normal group more often than in either diabetic group The differences are statistically significant (p < 0 01)

Need-persistence

GF	= 23.5 %	t = 0.342	p > 0 10
P	= 22.6 %	t = 0 437	p > 0 10
Normal group	= 26 4 %		

The solution of the frustrating problem is emphasized in the responses of children in the Normal group more often than in either diabetic group The children in the GF group come closer to the Normal group than the children in the P group do The differences are not statistically significant.

The only statistically significant difference between the Normal group and the diabetic groups is found in Reaction Types In frustrating situations the children in the Normal group are more ego-defensive i.e more person-oriented than the diabetic children.

The Holtzman Inkblot Technique

The Holtzman Inkblot Technique (HIT) is a new projective method which resembles the Rorschach but differs from it in several respects Unlike the Rorschach which has ten inkblots the HIT consists of two parallel forms A and B each of which contains 45 inkblots constituting the test series plus two practice blots X and Y The instructions given to the subject emphasize the following points

1) these inkblots were not made to look like anything in particular

2) different people see different things in each inkblot

3) only one response for each card is desired.

The responses are scored in terms of the following 22 variables

Reaction Time (RT) Rejection (R) Location (L) Space (S) Form Definiteness (FD) Form Appropriateness (FA) Color (C) Shading (Sh) Movement (M) Pathognomonic Verbalization (V) Integration (I) Human (H) Animal (A) Anatomy (At) Abstract (Ab) Anxiety (Ax) Hostility (Hs) Barrier (Br) Penetration (Ph) Balance (B) and Popular (P)

For the analysis of the above mentioned scores the method of *Discrimination Analysis* was used in this study

The results of the Discrimination Analysis are presented in Tables 30—32

Table 30 The Mean Values and the Standard Deviations on the Discriminat Line

	GF	P
Mean	0.32603	0.02331
Standard Deviation	0 07243	0 07206

Table 31 shows *the Discrimination Points* and the *Group Rank* of each diabetic subject

T ble 31 The Discrimination Point and the Group Rank of each subject.

Group Rank	Discrimination Points	Diabetic Control
1	0 50053	GF
2	0 44840	
3	0 41681	
4	0 39667	
5	0.37545	
6	0 37244	
7	0 36888	
8	0 36459	
9	0.35717	
10	0 34661	
11	0 34016	
12	0 32926	
13	0 32884	
14	0 32289	
15	0 32275	
16	0 31859	
17	0.31236	
18	0 31133	
19	0 30981	

Discussion

The aim of the present study was to discover both the immediate reactions and later adjustment of diabetic children and their parents to the diagnosis of the disease. A special endeavor was made to detect any possible correlations between the various coping processes and the degree of diabetic control

The reported results concern mainly the GF group in relation to the P group.

1 *Average age at diagnosis of diabetes* was significantly higher in the GF group than in the P group In the cases studied in this material, all the children who had developed diabetes prior to the age of three had poor control of their disease.

2 *The duration of the illness* in the GF group was significantly shorter than in the P group

3 In the series diabetes was *evenly distributed among males and females* in both the GF group and the P group

4 Studies of childhood diabetes have clearly demonstrated that diabetes is a *recessive hereditary disease* 20 % of the juvenile diabetic having known diabetic relations at the time of the diagnosis of their disease In the series 37 of the 60 diabetic children (63 %) had relatives known to be diabetic at the time when the whole series had been collected

The high percentage of diabetic relatives in this series can be explained at least partly by the facts that between the time of the first diagnosis and the last examination 1) new cases of diabetes manifested among the child relatives and 2) cases of diabetes among more distant perhaps already deceased relatives came to the parents knowledge

Pigoon and co-workers in their review of the available data concerning the hereditary transmission of diabetes come to the conclusion that the clinically primary diabetes has a reliable genetic ground and they support the hypothesis of multifactorial heredity According to their opinion it is probable that the main gene affects the insular function and is conveyed by means of an intermediate hereditary process The additional genes could act in promoting the passage from a prediabetic status to latent or clear diabetes. This passage is conditioned by environmental factors too (11)

5 Much has been written about *the growth of diabetic children.* Many authors remarked that *height was above normal at the time of diagnosis.* (44 57) As for ultimate adult stature, most studies over the past twenty-five years indicate that the average heights of both diabetic sexes are below normal, probably because of uniform presence of those 5 to 10 per cent with stunted growth Knowles and co-workers observed that men and women diabetics were two and one tenth, and one and one-tenth inches respectively shorter than their normal controls. Decrease in stature *was mainly in those with diabetes diagnosed before the growthspurt years.* (81)

Larsson and Sterky pointed out that in their Swedish study of juvenile diabetics who had reached *adulthood, in 12.9 per cent of men* and 3 3 per cent of women the height was below the *lower normal limit.* No *explanation was found* for the tendency towards short stature of these *patients They did not deviate from the rest of the* cases with regard to age at onset, duration, *chronological age food habits* blood *sugar level,* insulin requirements or extent of vascular damage. (88)

The presence of stunted growth at the time of last *examination in this series is 13.3 % (3.3* % in the GF group and 23.3 % in the P *group)*

The figures are too small for statistical *evaluation. Moreover* they cannot be considered as final because the majority of the have not yet reached adult *stature.* A tendency is, however for the heights to be below the lower normal limit *more often in* the P group than in the GF group

6 Swift and co-workers found that *the birth rank* of the childhood diabetic was significantly associated with the diabetic control. In their sample, in contrast to the present study the eldest child in the family had significantly worse control than did children of other birth *rank* (135) According to the findings of this study

accounts for more variance than the other Anxiety and Hostility may also have moderately high loadings on Factor I particularly among children A high amount of this factor would b- indicative of well organized ideational activity good imaginative capacity well differentiated ego boundaries and awareness of conventional concepts

Fartor II Percepual Sensit'vity

Defined primarily by Color and Shading this factor involves sensitivity to the stimulus qualities of the blots Reactions to Color o Shading are indicators of affective responsiveness and rich fantasy life

To summarize The children in the GF group according to the HIT results, have more integrated more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts.

In addition the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group

Discussion

The aim of the present study was to discover both the immediate reactions and later adjustment of diabetic children and their parents to the diagnosis of the disease. A special endeavor was made to detect any possible correlations between the various coping processes and the degree of diabetic control.

The reported results concern mainly the GF group in relation to the P group.

1 *Average age at diagnosis of diabetes* was significantly higher in the GF group than in the P group. In the cases studied in this material, all the children who had developed diabetes prior to the age of three had poor control of their disease.

The duration of the illness in the GF group was significantly shorter than in the P group.

3 In the series diabetes was *evenly distributed among males and females* in both the GF group and the P group.

4 Studies of childhood diabetes have clearly demonstrated that diabetes *is a recessive hereditary disease*. 20 % of the juvenile diabetics having known diabetic relations at the time of the diagnosis of their disease. In the series 37 of the 60 diabetic children (63 %) had relatives known to be diabetic at the time when the whole series had been collected.

The high percentage of diabetic relatives in this series can be explained, at least partly, by the facts that between the time of the first diagnosis and the last examination 1) new cases of diabetes manifested among the child's relatives and 2) cases of diabetes among more distant, perhaps already deceased relatives came to the parents' knowledge.

Rgozzi and co-workers in their review of the available data concerning the hereditary transmission of diabetes come to the conclusion that the clinically primary diabetes has reliable genetic ground and they support the hypothesis of multifactorial heredity. According to their opinion it is probable that the main gene affects the insular function and is conveyed by means of an intermediate hereditary process. The additional genes could act in promoting the passage from a prediabetic status to a latent or clear diabetes. This passage is conditioned by environmental factors, too. (11)

5 Much has been written about *the growth of diabetic children*. Many authors remarked that height was above normal at the time of *diagnosis*. (44 57) As for ultimate adult stature most studies over the past twenty five years indicate *that the average heights* of both diabetic sexes are below normal probably because of uniform presence of those 5 to 10 per cent with stunted growth. Knowles and co-workers observed that men and women diabetics were two and one tenth, and one and one-tenth inches respectively *shorter* than their normal controls. Decrease in stature was mainly in those with diabetes diagnosed before the *growthspurt years*. (81)

Larsson and Sterky pointed out that, in their Swedish study of juvenile diabetics who had reached adulthood, in 12.9 per cent of men and 3.3 per cent of women the height was below the lower normal limit. No *explanation was found* for the tendency towards short stature of these patients. They did not deviate from the rest of the cases with regard to age at onset, duration, chronological age, food habits blood sugar level insulin requirements or extent of vascular damage. (88)

The presence of stunted growth at the time of last examination in this series is 13.3 % (3.3 % in the GF group and 23.3 % in the P group).

The figures are too small for statistical evaluation. Moreover they cannot be considered as final because the majority of the have not yet reached adult stature. A tendency is, however, for the heights to be below the lower normal limit more often in the P group than in the GF group.

Swift and co-workers found that *the birth rank* of the childhood diabetic was significantly associated with the diabetic control. In their sample in contrast to the present study the eldest child in the family had *significantly* worse control than did children of other birth rank. (135) According to the findings of this study

accounts for more variance than the other Anxiety and Hostility may also have moderately high loadings on Factor I particularly among children. A high amount of this factor would b- indicative of well organized, ideational activity good imaginative capacity well differentiated ego boundaries and awareness of conventional concepts

Factor II Perceptual Sensitivity

Defined primarily by Color and Shading this factor involves sensitivity to the stimulus qualities of the blots Reactions to Color o Shading are indicators of affective responsiveness and rich fantasy life.

To summarize The children in the GF group according to the HIT results have more integrated more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts.

In addition the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group

Discussion

The aim of the present study was to discover both the immediate reactions and later adjustment of diabetic children and their parents to the diagnosis of the disease. A special endeavor was made to detect any possible correlations between the various coping procedures and the degree of diabetic control.

The reported results concern mainly the GF group in relation to the P group.

1 *Average age at diagnosis of diabetes* was significantly higher in the GF group than in the P group. In the cases studied in this material all the children who had developed diabetes prior to the age of three had poor *control of their disease*.

2 The *duration of the illness* in the GF group *was significantly shorter than in the P group*.

3 In the series diabetes *was evenly distributed among males and females* both the GF group and the P group.

4 Studies of childhood diabetes have clearly demonstrated that diabetes is *a recessive hereditary disease*. 20 % of the juvenile diabetic having known diabetic relations at the time of the diagnosis of their disease. In the series 37 of the 60 diabetic children (63 %) had relatives known to be diabetic at the time when the *whole* series had been collected.

The high percentage of diabetic relatives in this series can be explained, at least partly, by the facts that between the time of the first diagnosis and the last examination 1) new cases of diabetes manifested among the child's relatives and 2) cases of diabetes among more distant, perhaps already deceased relatives came to the parents' knowledge.

Rosen and co-workers in their review of the available data concerning the hereditary transmission of diabetes come to the conclusion that the clinically primary diabetes has reliable genetic ground and they support the hypothesis of a multifactorial heredity. According to their opinion it is probable that the main *gene affects* the insular function and is conveyed by means of an intermediate hereditary process. The additional genes could act in promoting the passage from a prediabetic status to a latent or clear diabetes. This passage is conditioned by environmental factors too. (11)

5 Much has been written about *the growth of diabetic children*. Many authors remarked that height was above normal at the time of diagnosis. (44 57) As for ultimate adult stature most studies over the past twenty-five years indicate that the average heights of both diabetic sexes are below normal probably because of uniform presence of those 5 to 10 per cent with stunted growth. Knowles and co-workers observed that men and women diabetics were two and one-tenth, and one and one tenth inches respectively shorter than their normal controls. Decrease in stature was mainly in those with diabetes diagnosed before the growthspurt years. (81)

Larsson and Sterky pointed out that, in their Swedish study of juvenile diabetics who had reached adulthood, in 12.9 per cent of men and 5.3 per cent of women the height was below the lower normal limit. No explanation was found for the tendency towards short stature of these patients. They did not deviate from the rest of the cases with regard to age at onset, duration, chronological age, food habits, blood sugar level, insulin requirements or extent of vascular damage. (88)

The presence of stunted growth at the time of last examination in this series is 13.3 % (3.3 % in the GF group and 23.3 % in the P group).

The figures are too small for statistical evaluation. Moreover they cannot be considered as final because the majority of the have not yet reached adult stature. A tendency is however for the heights to be below the lower normal limit more often in the P group than in the GF group.

6 Swift and co-workers found that *the birth rank* of the childhood diabetic was significantly associated with the diabetic control. In their sample, in contrast to the present study the *eldest child* in the family had significantly worse control than did children of other birth rank (135). According to the *findings* of this study

the eldest child's diabetes is rarely poorly controlled The discrepant findings of this study may be due to the limited sample or to other factors e.g cultural ones

7 In this study *the social status of the family* seems to be correlated with the diabetic control. The Social Groups I and II were more frequently found in the P group than in the GF group

8 The incidence of *mothers gainfully employed* was small in each diabetic group when compared with the over all incidence of gainfully employed married women in Finland. The difference can be partly explained by the restrictions caused by the child's illness partly by the fact that our Children's Hospital serves a large number of country communities where — for many reasons — the mothers can not go to work away from the home as easily as the mothers in cities and industrial centers.

There were more mothers working away from home in the P group than in the GF group The difference however is not statistically significant.

9 The assessment of *the family situation and the parents' mental and psychosomatic health* gave the following evaluation

All the diabetic children in this series seem to come from relatively stable homes This appraisal is based on relatively few contacts with the parents however

The incidence of emotional disturbances and psychosomatic conditions in the parents was about the same in the two diabetic groups

10 There are 2 children in the GF group and 6 in the P group who exhibited *neurotic or characterological symptoms* before the diagnosis of diabetes. The figures are too small for statistical evaluation On the other hand these figures are only minimum ones because they include only those symptoms which the parents were aware about and worried at the time of the diagnosis of the child's diabetes It is a general observation that the mental symptoms in young children often pass unnoticed by the parents or are attributed to the child's normal immaturity This is especially true of the two-year-olds of which there were 7 in the P group

11 According to the findings of this study *the incidence of stressful situations* was about the same in the two diabetic groups In three cases, one belonging to the GF group and two to the P group either the mother or the child spontaneously connected the event with the onset of the child's diabetes

Emotional stress is a widely discussed topic in both popular and scientific writing, often with no attempt to define what is meant.

In this paper the term "emotional stress" has the meaning given by Engel (40) and Stenbäck (130) Engel offers this definition "Psychological stress refers to all processes whether originating in the external environment or within a person, which impose a demand or requirement upon the organism the resolution of which requires activity of the mental apparatus before any other system is involved or activated Stenbäck uses the term "life stress" to describe all things in the life of the patient which the patient himself experiences as "stress" or which by sociological investigation are established as circumstances producing disturbances in human life. Both authors draw a distinction between the initiator or producer which Engel names "psychological stress" and Stenbäck "life stress" and the effects, which Engel calls tension" and Stenbäck "internal experience of stress" In a child's life stress situations are usually those demanding independent action or implying separation from parents.

Goldner states that the roles of environmental influence and of stress are relatively easy to determine where the onset of the disease is sudden and readily recognizable and where the etiological mechanisms are known. In diabetes mellitus however we are dealing with a hereditary or genetic predisposition and moreover with a disease which usually has an inconspicuous and insidious onset Stressful life situations on the other hand, are common With some imagination one can find in each diabetic history coinciding with the first manifestation of the disease, an event which could be described as a causative stress. Critical analysis however will show that similar events occur just as frequently in the histories of healthy people and non-diabetic patients Only careful case analysis of the specific aspects of an individual case, with proper consideration of the past history the severity the duration of the stress situation and its proximity to the manifestation of the diabetes, can reveal the probability of a causal relationship. (51)

With these reservations in mind, one quickly realizes that in a research project like the present a detailed analysis of each case cannot be made. The findings therefore only indicate a potential causality between the stress situation and the manifestation of diabetes mellitus

12 *The family's immediate reaction* to the illness of their child was often characterized by feelings of bewilderment and shock, anxiety fears and depressive feelings, which were often accompanied by feelings of guilt. In some instances the child' illness apparently brought out the parent's aggressive feelings, which were then directed towards the child or the persons in charge of the child's treatment. In some instances the parents consoled themselves with wishful thinking, usually imagining that their child' illness was not a chronic one.

The differences in the parent's immediate reactions between the two diabetic groups were mainly in the presence of initial insomnia and wishful thinking, which were more common in *mothers of the GF group* than in those of the P group. There is a general trend, although statistically nonsignificant, for the mothers in the GF *group to be more* emotional, vivid and colorful in their immediate reactions.

13 Whenever *diabetes* is diagnosed in a child, the family has to adjust itself to the child's chronic illness and the limitations and alterations this brings *into the day-to-day* life *of the family* At the same time, the members of the family have to learn how to handle their feelings of anxiety depression, etc Thus the adaptive processes take place at two different levels at the same time In this study these two-level adaptive processes are called *the external and internal coping processes* In terms of external coping it was found that constructive coping devices were much more common *in the* GF *group than in the* P group Accordingly non-constructive coping processes, mainly helplessness and poor co-operation in the daily care of the diabetic child, were more frequent findings in the P group

The main areas where the family's coping with the child' illness can be observed are the diabetic diet and the insulin injections. It was found that constructive coping apparently was greatly promoted by good co-operation and sharing of responsibility among members of the family Every one of those families in which other members of the family have adopted the child's diet belongs to the GF group Correspondingly to the GF group there are significantly more families in which more than one member takes share in giving the daily insulin injection.

One of the main objectives of this study was to comprehend some of the parents inner motivations, which could cause their external coping behavior Apparently all parents try to care for their diabetic child in the way which, in their judgement, is most beneficial for the child. It has been demonstrated elsewhere that difficulties in daily diabetic care are often the cause of lability and great shifts in the patient's metabolic state. (134)

In this study it was established that there was positive correlation between constructive external coping processes and constructive *internal* coping processes, which in this connection means ability to adequately work through and control the feelings of anxiety loss and depression. *In many* instances the parents find some enjoyment in caring for their sick child, who because of his sickness, remains more closely attached to the parents.

Correspondingly the non-constructive external coping devices show positive correlation with the non-constructive internal coping, in these cases mainly denial, omnipotent thinking, depression and phobias.

14 *The child's immediate reaction* to the discovery of diabetes could only be evaluated in those cases in which the child's first hospitalization occurred at the time of the study or in cases when either the mother or the hospital record provided sufficient data. Additionally it would require more detailed case studies to be able to differentiate between the child's reaction to his illness *and his reaction to the hospitalization*. However from the findings of this study it seems probable that the severity of the child' *first reaction does not relate to the later* controllability of his diabetes. It may even be that child who in the first stage of his illness *is able to give vent to his anxiety* can better work it through and become able to handle it later on.

15 *The child' later adjustment* was considered in terms of

a) the symptomatic reactions and

b) the general evaluation of his adjustment at home at school and in hospital and/or out patient department visits.

The symptomatic reactions exhibited by the children prompt the following remarks

A *Disturbances Related to Bodily Functions* There are 5 children in the GF group and 8 children *in the* P group who at the age of 4 were still enuretic.

the eldest child's diabetes is rarely poorly controlled. The discrepant findings of this study may be due to the limited sample or to other factors e.g. cultural ones.

7. In this study *the social status of the family* seems to be correlated with the diabetic control. The Social Groups I and II were more frequently found in the P group than in the GF group.

8. The incidence of *mothers gainfully employed* was small in each diabetic group when compared with the over all incidence of gainfully employed married women in Finland. The difference can be partly explained by the restrictions caused by the child's illness partly by the fact that our Children's Hospital serves a large number of country communities where — for many reasons — the mothers can not go to work away from the home as easily as the mothers in cities and industrial centers.

There were more mothers working away from home in the P group than in the GF group. The difference however is not statistically significant.

9. The assessment of *the family situation and the parents' mental and psychosomatic health* gave the following evaluation.

All the diabetic children in this series seem to come from relatively stable homes. This appraisal is based on relatively few contacts with the parents, however.

The incidence of emotional disturbances and psychosomatic conditions in the parents was about the same in the two diabetic groups.

10. There are 2 children in the GF group and 6 in the P group who exhibited *neurotic or characterological symptoms* before the diagnosis of diabetes. The figures are too small for statistical evaluation. On the other hand these figures are only minimum ones because they include only those symptoms, which the parents were aware about and worried at the time of the diagnosis of the child's diabetes. It is a general observation that the mental symptoms in young children often pass unnoticed by the parents or are attributed to the child's normal immaturity. This is especially true of the two-year-olds of which there were 7 in the P group.

11. According to the findings of this study *the incidence of stressful situations* was about the same in the two diabetic groups. In three cases, one belonging to the GF group and two to the P group, either the mother or the child spontaneously connected the event with the onset of the child's diabetes.

Emotional stress is a widely discussed topic in both popular and scientific writing, often with no attempt to define what is meant.

In this paper the term "emotional stress" has the meaning given by Engel (40) and Stenbäck (130). Engel offers this definition: "Psychological stress refers to all processes whether originating in the external environment or within a person, which impose a demand or requirement upon the organism, the resolution of which requires activity of the mental apparatus before any other system is involved or activated." Stenback uses the term "life stress" to describe all things in the life of the patient which the patient himself experiences as "stress" or which by sociological investigation are established as circumstances producing disturbances in human life. Both authors draw a distinction between the initiator or producer, which Engel names "psychological stress" and Stenback "life stress", and the effects, which Engel calls tension and Stenbäck "internal experience of stress". In a child's life stress situations are usually those demanding independent action or implying separation from parents.

Goldner states that the roles of environmental influence and of stress are relatively easy to determine where the onset of the disease is sudden and readily recognizable and where the etiological mechanisms are known. In diabetes mellitus, however, we are dealing with a hereditary or genetic predisposition and moreover with a disease which usually has an inconspicuous and insidious onset. Stressful life situations, on the other hand, are common. With some imagination one can find in each diabetic history coinciding with the first manifestation of the disease, an event which could be described as a causative stress. Critical analysis, however, will show that similar events occur just as frequently in the histories of healthy people and non-diabetic patients. Only careful case analysis of the specific aspects of an individual case with proper consideration of the past history, the severity, the duration of the stress situation and its proximity to the manifestation of the diabetes can reveal the probability of a causal relationship (51).

With these reservations in mind one quickly realizes that in a research project like the present a detailed analysis of each case cannot be made. The findings, therefore, only indicate a potential causality between the stress situation and the manifestation of diabetes mellitus.

12 *The family's immediate reaction* to the illness of their child was often characterized by feelings of bewilderment and shock, anxiety fears and depressive feelings, which were often accompanied by feelings of guilt. In some instances the child's illness apparently brought out the parent's aggressive feelings, which were then directed towards the child or the persons in charge of the child' treatment. In some instances the parents consoled themselves with wishful thinking, usually imagining that their child's illness was not a chronic one.

The differences in the parent's immediate reactions between the two diabetic groups were mainly in the presence of initial insomnia and wishful thinking, which were more common in mothers of the GF group than in those of the P group. There is general trend, although statistically nonsignificant, for the mothers in the GF group to be more emotional, vivid and colorful in their immediate reactions.

13 Whenever diabetes is diagnosed in a child, the family has to adjust itself to the child's chronic illness and the limitations and alterations this brings into the day-to-day lif of the family. At the same time, the members of the family have to learn how to handle their feelings of anxiety depression, etc. Thus the adaptive processes take place at two different levels at the same time In this study these two-level adaptive processes *are called the external and internal coping processes* In terms of external coping it was found that constructive coping devices were much more common in the GF group than in the P group Accordingly non-constructive coping processes, mainly helplessness and poor co-operation in the daily care of the diabetic child were more frequent findings in the P group.

The main areas where the family coping with the child' illness can be observed are the diabetic diet and the insulin injections. It was found that constructive coping apparently was greatly promoted by good co-operation and sharing of responsibility among members of the family Every one of those families in which other members of the family have adopted the child's diet belongs to the GF group Correspondingly in the GF group there are significantly more families in which more than one member takes share in *giving the daily insulin injection.*

One of the main objectives of this tudy was to comprehend some of the parents inner motivations, hich could cause their external coping behavior Apparently all parents try *to care for their diabetic child* in the way which, in their judgement, is most beneficial for the child. It has been demonstrated elsewhere that difficulties in daily diabetic care are often the cause of *lability* and great shifts in the patient's metabolic state. (134)

In this study t was established that there was a positive correlation between constructive external coping processes and constructive *internal coping* processes, which in this connection means ability to adequately work through and control the feelings of anxiety loss and depression. In many instances the parents find some *enjoyment in caring for their sick* child, who because of his sickness, remains more closely attached to the parents.

Correspondingly the non-constructive external coping devices show a positive *correlation with* the non-constructive internal coping, in these cases mainly denial omnipotent thinking, depression and phobias.

14 *The child's immediate action* to the discovery of diabetes could only be evaluated n those cases in which the child's first hospitalization occurred at the time of the study or in cases where either the mother or the hospital record provided sufficient data. Additionally it would require more detailed case tudies to be able to differentiate between the child's reaction to his illness and his reaction *to the hospitalization.* However from the findings of this study it seems probable that the severity of the child's first reaction does not relate to the later *controllability of his diabetes. It may* even be that child who in the first stage of his illness is able to give vent to his anxiety can better work it through and become able to *handle it later on.*

15 The *child's later adjustment* was considered in terms of

a) the symptomatic reactions and

b) the general *evaluation of his adjustment* at home at school and in hospital and/or out patient department visits.

The symptomatic reactions exhibited by the children prompt the following remarks

A. Disturbances Related to Bodily Functions. There are 5 children in the GF group and 8 children in the P *group who at the age of 4* were still enuretic.

Authors disagree about the exact age at which a child can be labeled as enuretic. In this study the figures reported by Bellman and Hallgren are used as comparative data (8 54) Both set the age limit for enuresis at 4 years

Bellman found the incidence of enuresis at an average age of $7^{3}/_{4}$ years to be 5.8 % In this study the number of children who were still enuretic at the age of 8 years was 7 (13 %)

Of the 13 children who were enuretic after the age of 4 10 were boys and 3 girls. This is in accordance with other studies which indicate that enuresis is more frequent in boys than in girls

Enuresis is generally regarded as a symptom with heterogeneous etiology Where diabetes is concerned both somatic and psychogenic factors related to enuresis should be considered

a) one of the more frequent symptoms of polyuria in diabetes is bedwetting.

b) enuresis sometimes develops after a physical illness especially if the examination or treatment procedures have centered around the genitourinary system In diabetes urinalysis is part of the daily routine Bedwetting might even in some cases be an unconscious way of escaping from the urinalysis if the child knows that he has eaten something forbidden.

c) in the literature enuresis is generally regarded as a sign of immaturity It is also thought that enuretic children have difficulty in handling their aggressions

In individual cases more than one of the above mentioned etiological factors may operate simultaneously

Speech and language disturbances were found only among the children belonging to the P group

B *Developmental Difficulties*

There was one case of excessive separation anxiety and one case of manifest problems in sexual identification both belonging to the P group

C. *Disturbances in Social Behavior*

Aggressive antisocial and oppositional behavior disturbances were found almost entirely in the P group This is especially true of oppositional behavior (passive resistance passive aggressive behavior disobedience and running away) which appears only in the P group Although the figures are too small for any far reaching conclusions antisocial and oppositional behavior can be singled out as behavior types specific to the P group

D *Disturbances in Affective Behavior*

In contrast to the oppositional behavior anxious behavior and manifestly fearful behavior were more frequent in the GF group than in the P group

E. *Difficulties in Integrative Behavior*

Difficulties in integrative behavior were found in 3 cases of the GF group and in 7 cases of the P group

In *the general evaluation* of the child's later adjustment it was discovered that normal adjustment and mild adjustment disorders were more frequent in the GF group than in the P group Accordingly psychoneurosis and personality trait disorders were more frequent in the P group

16 A greater proportion of children in the GF group were at the top of the form One fifth of the children in the P group had had to repeat a class in the elementary school, whereas this phenomenon had not occurred among the children in the GF group

17 The intelligence test revealed no statistically significant difference between the children in the GF group and those in the P group The distribution curves thus show good agreement with the average curve The investigation thus suggests that

a) intelligence is of no specific importance for diabetic control

b) the better academic success of the children in the GF group is apparently caused by factors other than intelligence

18 The Rosenzweig Picture Frustration Test analyzing the child's attitudes to different frustrating situations revealed no statistically significant differences between the two diabetic groups

When the diabetic children were compared with normal control subjects the findings were as follows

The only statistically significant difference between the normal group and the diabetic group was found in Reaction Types In frustrating situations the children of the normal group were

more ego-defensive and more person-oriented than the diabetic children.

18 The discrimination analysis of the Holtzman Inkblot Technique scores shows that the two diabetic groups differ clearly from each other on the Discriminant Line. There is only one exception, a child belonging clinically to the G⁻ group, whose Discrimination Points locate him in the middle of the P group.

For this series those best discriminating variables were Integration, Popular, Movement, Animal, Color, Shading, Barrier and Hostility. The major dimensions measured by these variables are as follows.

Holtzman Factor I Perceptual Maturity and Integrated Ideational Activity. A high amount of this factor would be indicative of well organized, ideational activity, good imaginative capacity, well differentiated ego boundaries, and awareness of conventional concepts.

Holtzman Factor II Perceptual Sensitivity

This factor involves sensitivity to the stimulus *qualities of the blots. Reactions to Color and* Shading are indicators of affective responsiveness and rich fantasy life.

According to the HIT results the children in the GF group have more integrated, more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts. In addition, the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group.

This study has disclosed a number of variables related to the control of childhood diabetes in this series. The findings of this study do not necessarily mean that the variables disclosed are independent ones. For example the age at the diagnosis was found to be significantly correlated with the control of diabetes, being earlier in the P group. At the same time, the mother's omnipotent thinking concerning the child's illness was found to be correlated with Poor Control of diabetes. But it is possible that the great dependency of a young child upon the mother is apt to evoke in the mother the feeling that the child's illness belongs entirely to her.

Accordingly if the child is *older at the* diagnosis of diabetes, he has already had a chance to establish himself as a separate individual with responsibility for his own body and illness. It can be argued that this phenomenon is also apparent in the HIT results, where the children in the GF group give responses indicating significantly better integrated ego-boundaries.

In the light of these results it might be useful to re-examine the techniques that *have been* developed to meet the emotional needs of families of diabetic children. The first step in many cases might be the confrontation and reduction of the child's anxiety and also the parents'. In the light of this study it seems that when the mother's anxiety and depression had not been adequately dealt with at the start, they tended to affect her ability to cope with the child's illness.

Educative efforts are provided by all clinics treating diabetic children. The aim is to teach the parents and children about diabetes. But these efforts should be geared so that the anxiety and depression are at least somewhat relieved before the education is offered.

In the light of this study it *seems important* to stress the value of the co-operation of all members of the family in the care of the child's diabetes. *Understandably it is hard to teach the* child self-care of insulin injections if one or more members of the family morbidly fear the injections. Swift and co-workers have concluded that too often the fact that the child with diabetes is different is denied, and the child has been assured that he is *no different* (135). These *impressions are in agreement with the* findings of this study where massive denial of the child's illness was found to be positively correlated with Poor Control of the child's diabetes. A confrontation aimed at securing the honest admission that the child has chronic disease which makes him different from his healthy age-mates, combined *with highlighting* the intact areas of functioning, seem to aid the family in achieving the best overall adjustment and at the same time better control of the child's diabetes.

Authors disagree about the exact age at which a child can be labeled as enuretic. In this study the figures reported by Bellman and Hallgren are used as comparative data (8 54). Both set the age limit for enuresis at 4 years.

Bellman found the incidence of enuresis at an average age of 7[3]/4 years to be 5 8 %. In this study the number of children who were still enuretic at the age of 8 years was 7 (13 %).

Of the 13 children who were enuretic after the age of 4 10 were boys and 3 girls. This is in accordance with other studies which indicate that enuresis is more frequent in boys than in girls.

Enuresis is generally regarded as a symptom with heterogeneous etiology. Where diabetes is concerned, both somatic and psychogenic factors related to enuresis should be considered

a) one of the more frequent symptoms of polyuria in diabetes is bedwetting.

b) enuresis sometimes develops after a physical illness especially if the examination or treatment procedures have centered around the genitourinary system. In diabetes urinalysis is part of the daily routine. Bedwetting might even in some cases be an unconscious way of escaping from the urinalysis if the child knows that he has eaten something forbidden.

c) in the literature enuresis is generally regarded as a sign of immaturity. It is also thought that enuretic children have difficulty in handling their aggressions.

In individual cases more than one of the above mentioned etiological factors may operate simultaneously.

Speech and language disturbances were found only among the children belonging to the P group.

B *Developmental Difficulties*

There was one case of excessive separation anxiety and one case of manifest problems in sexual identification both belonging to the P group.

C. *Disturbances in Social Behavior*

Aggressive antisocial and oppositional behavior disturbances were found almost entirely in the P group. This is especially true of oppositional behavior (passive resistance passive-aggressive behavior disobedience and running away) which appears *only* in the P group. Although the figures are too small for any far reaching conclusions antisocial and oppositional behavior can be singled out as behavior types specific to the P group.

D *Disturbances in Affective Behavior*

In contrast to the oppositional behavior anxious behavior and manifestly fearful behavior were more frequent in the GF group than in the P group.

E. *Difficulties in Integrative Behavior*

Difficulties in integrative behavior were found in 3 cases of the GF group and in 7 cases of the P group.

In *the general evaluation* of the child's later adjustment it was discovered that normal adjustment and mild adjustment disorders were more frequent in the GF group than in the P group. Accordingly psychoneurosis and personality trait disorders were more frequent in the P group.

16 A greater proportion of children in the GF group were at the top of the form. One fifth of the children in the P group had had to repeat a class in the elementary school whereas this phenomenon had not occurred among the children in the GF group.

17 The intelligence test revealed no statistically significant difference between the children in the GF group and those in the P group. The distribution curves thus show good agreement with the average curve. The investigation thus suggests that

a) intelligence is of no specific importance for diabetic control

b) the better academic success of the children in the GF group is apparently caused by factors other than intelligence.

18 The Rosenzweig Picture Frustration Test analyzing the child's attitudes to different frustrating situations revealed no statistically significant differences between the two diabetic groups.

When the diabetic children were compared with normal control subjects the findings were as follows

The only statistically significant difference between the normal group and the diabetic group was found in Reaction Types. In frustrating situations the children of the normal group were

more ego-defensive and more person-oriented than the diabetic children.

18 The discrimination analysis of the Holtzman Inkblot Technique scores shows that the two diabetic groups differ clearly from each other on the Discriminant Line. There is only one exception, child belonging clinically to the GP group, whose Discrimination Points locate him in the middle of the P group.

For this series those best discriminative variables were Integration, Popular Movement, Animal, Color Shading, Barrier and Hostility. The major dimensions measured by these variables are as follows

Holtzman Factor I Perceptual Maturity and Integrated Ideational Activity. A high amount of this factor would be indicative of well organized, ideational activity good imaginative capacity well differentiated ego boundaries, and awareness of conventional concepts

Holtzman Factor II Perceptual Sensitivity

This factor involves sensitivity to the stimulus qualities of the blots Reactions to Color and Shading are indicators of affective responsiveness and rich fantasy life

According to the HIT results the children in the GP group have more integrated, more imaginative personalities with better differentiated ego-boundaries and more awareness of conventional concepts. In addition the rather high negative coefficients of Movement and Hostility suggest higher aggressiveness in the children of the P group

This study has disclosed number of variables related to the control of childhood diabetes in this series. The findings of this study do not necessarily mean that the variables disclosed are independent ones. For example the age at the diagnosis was found to be significantly correlated with the control of diabetes, being earlier in the P group. At the same time the mother omnipotent thinking concerning the child' illness was found to be correlated with Poor Control of diabetes. But it is possible that the great dependency of young child upon the mother is apt to evoke in the mother the feeling that the child' illness belongs entirely to her. Accordingly if the child is older at the diagnosis of diabetes, he has already had chance to establish himself as a separate individual with a responsibility for his own body and illness. It can be argued that this phenomenon is also apparent in the HIT results where the children in the GP group give responses indicating significantly better integrated ego-boundaries.

In the light of these results t might be useful to re-examine the techniques that have been developed to meet the emotional needs of families of diabetic children. The first step in many cases might be the confrontation and reduction of the child' anxiety and also the parent s. In the light of this study it seems that when the mother anxiety and depression had not been adequately dealt with t the start they tended to affect her ability to cope with the child's illness

Educative efforts are provided by all clinics treating diabetic children. The aim is to teach the parents and children about diabetes. But these efforts should be geared so that the anxiety and depression are at least somewhat relieved before the education is offered

I the light of this study it seems important to stress the value of the co-operation of all members of the family in the care of the child's diabetes Understandably it is hard to teach the child self-care of insulin injections if one or more members of the family morbidly fear the injections. Swift and co-workers hav concluded that too often the fact that the child with diabetes is different is denied, and the child has been assured that he is no different (135) These impressions are in agreement with the findings of this study where massive denial of the child's illness was found to be positively correlated with Poor Control of the child's diabetes. A confrontation aimed at securing the honest admission that the child has a chronic disease which makes him different from his healthy age mates, combined with highlighting the intact areas of functioning, seem to aid the family in achieving the best overall adjustment and at the same time better control of the child's diabetes.

Summary

The aim of the present study was to search for both the immediate reactions to the diabetes and the more permanent coping processes in diabetic children and their parents. A special attempt was made to detect possible *correlations* between the various external and internal coping processes and the adequacy with which the diabetes was controlled.

In addition to the above-mentioned aim of the study the investigation was concerned with a number of factors affecting diabetic control both medical social and socio-psychiatric. The *investigation was* conducted on 60 diabetic children and their parents Of these 60 children 30 had Good of Fair Control (GF) and 30 had Poor Control (P) of the diabetes. The criteria of diabetic control were in terms of growth acetonuria, 24-hour quantitative urine glucose fasting blood sugar and number of hospitalizations per year

The investigation involved interviews and play observations with the children and interviews with the parents. One interview with each parent was a structured one, in which a special questionary was gone through

Estimates of the children's scholastic achievements adjustment to school and teachers and relations with peers were obtained from their teachers

The psychological examination of each child comprised an intelligence test of Stanford-Binet type (Terman-Merrill Lehtovaara) and two personality tests (Rosenzweig Picture Frustration Test and Holzman Inkblot Technique)

Medical data on the children were collected from their hospital and out patient records Those childen who were hospitalized during the time of collecting the series (September 1964 — December 1967) were observed on the ward and in group situations At the same time observations were made on parent-child interactions during visiting hours

The family's immediate reaction to the illness of their child was often characterized by feelings of bewilderment and shock anxiety fears and depressive feelings. Initial insomnia and wishful thinking were more common in mothers of the GF group than in those of the P group There is a general trend, although non-significant statistically for the mothers in the GF group to be more emotional and vivid in their immediate reactions

The external coping processes were more constructive in the GF group than in the P group On the other hand non-constructive coping processes mainly helplessness and poor co-operation in the daily care of the diabetic child were frequent findings in the P group

It was found that constructive coping apparently was greatly promoted by good co-operation between all members of the family and shared responsibility for seeing that the child followed the correct regimen.

The constructive internal coping processes which in this connection means the ability to adequately work through and control the feelings of anxiety loss and depression were found to be positively correlated with constructive external coping processes. On the other hand, the way in which the P group families inwardly coped with the anxiety and depression showed more pathological and extreme forms mainly denial, omnipotent thinking chronic underlying depression and phobias.

The child's immediate reaction to the discovery of diabetes could not be evaluated in all cases. The findings of this study do not suggest that the severity of the child's first reaction determines the later controllability of his diabetes.

The children in the GF group had fewer and less pathological ***symptomatic reactions*** and better ***later adjustment*** than the children in the P group The P group was found to be more extreme and/or pathological in the number of symptomatic reactions as well as in the psychiatric clinical ratings

The GF group showed better ***academic achievement*** than the P group

Statistical analyses showed no differences between the two diabetic groups in terms of hereditary predisposition to diabetes family size, I Q of the children or the results in the Rosenzweig Picture Frustration Test

Statistical differences were found *in the age of first diagnosis of diabetes* and *in the duration of the illness*. In addition, the two groups were significantly or almost significantly alike in *social class* of the family and *birth rank* of the diabetic child. On independently scored *Holtzman Inkblot Technique* data, the GF group showed better organized ideational capacity better differentiated ego-boundaries and more imaginative and sensitive personalities. On the other hand, the P group showed less integrated, less imaginative and less sensitive personalities with more pathological ego boundaries and stronger aggressiveness.

Acknowledgements

I am indebted to the late Professor Toivo Salmi M D Children's Hospital University of Turku who started the child psychiatric services at the Clinic headed by him and followed the early phase of my work with keen interest

Professor Tuomas Peltonen, M D Head of the Children's Hospital University of Turku has unfailingly encouraged and stimulated my work with interest and objectivity It is hard to find words to express my gratitude to him

Professor Asser Stenback M. D in the preparatory phase of this study supplied me with valuable advice based on his thorough knowledge of psychiatric research My best thanks are due to him

My thanks are also due to Dr Elsa Brita Nordlund child psychiatrist Karolinska Sjukhuset Stockholm who read my typescript and gave me valuable comments and advices based on her knowledge and experience in the field of child psychiatry

Mr Penttu Sinisalo and Mr Tapio Korhonen Mag. Phil performed the psychological examinations of the children I am grateful for their valuable co-operation

I am grateful to Mr Pekka Lehtiö Mag Phil who made the statistical analyses and programmed the data processing

Mrs Aili Ryynänen M A and her assistants at the Library of the Medical Faculty University of Turku helped me in collecting the literature. My sincere thanks are due to them

Mrs Inkeri Perälä the occupational therapist, who observed the children in group situations, has contributed greatly to the data.

Mrs Jean Margaret Perttunen B Sc and Mr Sidney D Berger have revised the language of the manuscript In addition to this they have given me valuable advice and support for which I am deeply grateful to them

I wish to express my gratitude to the personnel of the Children's Hospital for their assistance during the study

My sincere thanks are also due to the families who participated in this study

The investigation was supported by grants from the Foundation for Pediatric Research in Finland from the Yrjö Jahnsson Foundation and from the Psychiatric Association in Finland

Here I wish to acknowledge their valuable support

Last but not least I wish to thank my 4 sons who have shared the burden of the work with me and who have taught me much about coping in stressful life situations

Loppi August 1969

Maija-Liisa Koski

References

1 *Ack, M I and Weil W B J* Intelligence of children with diabetes mellitus Pediatrics, 28 764, 1961

2 *Alexander* F Psychosomatic Medicine W W Norton New York, 1950

3 Bauch M Beeinflussung des Diabetes Mellitus durch psychophysische Entspannungsübungen Deutsch Arch f klin Med, 178 149 1933

4 *Bowland* J T J A case of attempted suicide in diabetes J A M A 102 765 1934

5 *Bauer S B* Diabetes mellitus New Engl J Med 251 757 1954

Beck, S J and Nunnally C J Parental attitudes in families Arch Gen Psychiat, 13 208, 1965

7 *Beck, A T Ward C H Mendelson M Mock J and Erbaugh J* An inventory for measuring depression Arch Gen Psychiat 4 561 1961

8 Bellman M Studies on encopresis Acta Paed at Scand Supp 170 1966

9 Benedek T An approach to the study of the diabetic Psychosom Med 10 284, 1948

10 Bennett E M *and* Johannsen D E Psychodynamics of the diabetic child Psychol Monogr 68 1 1954

11 *Bonetti U and Tondury U* Il problema dell' eredita del diabete English summary Acta diab latina, 2 175 1965

12 Boller R Diabetes mellitus Urban & Schwarzenberg Wien, 1950

13 Boudreau E H Psychic states associated with hypoglycemia New York State J Med 57 1627 1934

14 Boulin J Pathological mourning and childhood mourning J Amer Psychoanal Ass, 11 500 1963

15 Brown G D The development of diabetic children with special reference to mental and personality comparisons Child Devel 9 175 1938

16 Brown G D and Thompson W H The diabetic child an analytic study of his development Am J Dis Child 59 238 1940

17 *Bruch H and Hewlett I* Psychologic aspects of the medical management of diabetes in children Psychosom Med 205 1947

18 *Bruch H* Physiologic and psychologic interrelationships in diabetes in children Psychosom Med, 11 200 1949

19 *Cohen A S Vance V K Runyan, J W and Hurwitz, D* Diabetic acidosis an evaluation of the cause, course and therapy of 73 cases Ann Int Med 52 55 1960

20 Crowell *D H* Personality and physical disease test of the Dunbar hypothesis applied to diabetes mellitus and rheumatic fever Genet Psychol Monogr 48 117 1953

21 *Dahlberg, G Jorpes E Kallner S and Lichtenstein, A* Diabetes mellitus in Sweden Acta Med Scand Supp 188 1947

22 *Dahlberg, G* Familiebegreber and Diabetes Acta Paediat scand, 38 91 1949

23 Daniels G E Emotional and instinctual factors in diabetes mellitus Am J Psychiat, 93 711 1936

24 Daniels G E Analysis of case of neurosis with diabetes mellitus Psychoanal Quart, 5 513 1936

25 Daniels G E Present trends in the evaluation of psychic factors in diabetes mellitus Psychosom Med, 1 527 1939

26 Daniels, G E The role of emotion in the onset and course of diabetes Psychosom Med, 10 288, 1948

27 *Danowski T S Greenman L Weigand F A and Mateer F M* Acidosis and coma in juvenile diabetes. Am J Dis Child, 93 541 1957

28 Danowski T S Emotional stress as cause of diabetes mellitus Diabetes, 12 183 1963

29 *Deshaelf* quoted by Menninger (93)

30 *Dean D M Shipp J C and Pattishall E G* Attitudes of diabetic boys and girls towards diabetes Diabetes, 14 106, 1965

31 Debec B *Kronsilberchi, M and Margolis A* The psychic peculiarities of diabetic child Pediat Polska, 37 1287 1962

32 Deutsch F The psychosomatic concept in psychoanalysis Internat Univ Press New York, 1953

33 Dobbins *H L Lipscomb H S Greene J A and Engelhardt H T* Socioeconomic status and diabetes mellitus J Chronic Dis, 7 433 1958

34 Dunbar F *Wolfe T P and Rioch J McK* Psychiatric aspects of medical problems Am J Psychiat, 93 649 1936

35 Dunbar F Psychosomatic diagnosis Hoeber New York, 1948

36 Dunbar F Emotions and bodily changes Columbia University Press, New York, 1954.

37 Duke S P A dental study of children with pulmonary tuberculosis Amer J Orthopsychiat, 20 520 1950,

38 Enide *H B* The juvenile diabetic surviving 20 years JAMA, 120 188, 1942.

39 *Etzwiler D D and Sines L K.* Juvenile diabetes and its management family social and academic mplications JAMA 181 304 1962.

40 *F gel G L.* Homeostasis, behavioral adjustment and the concep of he lth and disease Mid-century Psychiat Ed. by Grinker Charles C Thomas, Springfie d 1953

41 *L gl son G* Diabetes mellitus. Nordisk laerobog I paediatri 5th ed, M nksgaard, Copenhagen 1952.

42 *alster E I and J das I* Juvenile diabetes and its psychiat c mplications. Am J Orthopsychiat 25 350 1955

43 *I nch S M and Hess J* Ulcerative coliti in children Am J Psychiat, 118 819 1962.

44 *F scher A E and Dolger H* Beha ior and psychological problems of young diabetic patients. Arch Int Med, 78 711 1946.

45 *Fischer A E* Factors responsible for emotional disturbance in diabetic children. Nervous Child, 7 78, 1948.

46. *Friedman S B Mason J W and Hamburg, D A* Urinary 17-hydrocorticosteroid leve s in parents of children with neoplastic disease. Psychosom Med, 25 364 1963

47 *Freud* A Role of bodily illness in mental lif of hildren. Psychoanal Stud Child, 7 69 1952.

48. *Gamstorp I Shelburne S A J Engleson G Redondo D and T aitmen H S* Periphera neuropathy j venile diabetes Diabetes 15 411 1966

49 *Gerst H* The psychological aspects of diabetes Charles C Thomas, Spr ngfield, 1964

50 *Gendel B R and Benjamin J E* Psychogenic factors I the etiology of diabetes New England J Med, 234 556 1946

51 *Goldner M C* Stress, corticoids and diabetes Diabetes 7 410 1958

52 *Goodman J I Schwartz, E D and F ankel L* Group therapy of obese diabetic patients Diabetes, 2 280 1953

53 *Greenberg, A and Blair J L* Social aspects of diabetes mellitus Diabetes 2 272 1953

54 *Hallgren B* Enuresis I A study with reference t the morbidity sk and symptomatology Acta Psychia Neurol Scand 31 379 1956.

55 *Harris M M* Metabolic consideration regardin psychoses. Arch Neur Psychiat 31 881 1934

56 *Helsingi Kaupun sin islastotoimisto* Sos aalitilyhteys 1965

57 *Hernberg, C A and Heikel P E* The skeletal age diabetic children. Acta Paediat Scand 40 486 1951

58 *Hershowitz H* A psychiatrist view of diabetes mellitus Am Dietetic Ass J 12 40 1936

59 *Hinkle L E J Evans F M and Wolf S* Studies on diabetes mellitus. Psychosom Med, 13 160, 1951

60 *Hinkle L E J and Wolf S* The effect of stressful lif situations on the concentration of blood glucose in diabetic and nondiabet humans. Diabetes, 1 383 1952.

61 *Hi kle L E J and Wolf S* A summary of experimental evidence relating life stress to diabetes mellitus. J Mt Sinai Hosp 19: 537 1952

62. *Hinkl L E J and Wolf S* Importance of l stress in course and management of diabetes mellitus AMA 148. 513 1952.

63 *Hinkle L E J* The doctor patient relationship in the management of diabetic patients and their emotional problems. New York J Med, 53 1943 1953

64 *H kle L E J* The Influence of the patient's behaviour and his reaction to his life tuation upon the course of diabetes. Diabetes, 5 406, 1956.

65 *Hinkle L E J Fischer A Knowles, H C Jr and Stunkard A J* Role of environment and personality in management of the difficult patient with diabetes mellitus Diabetes, 8 371 1959

66 *H kle J E J* Customs, emotions and behavio l the dietary treatment of diabetes. J Amer Diet Ass, 41 341 1962.

67 *Holtzman W H* Holtzman Inkblot Technique. Mc Graw Hill Co 1967

68 *Holtzman W H* Holtzman I kbot Technique. Draft Copy 1966.

69 *Holtzman W H* Cross cultural research on personality development Human Devel 8 65 1965

70 *Holcomb B* The responsibilities of the diabetic physician Diabetes 3 328 1954

71 *Jacobson E* Progressi relaxation 2nd ed. The University of Chicago Press Chicago, 1939

72 *Jessner L Blom G and Waldfogel S* Emotional mplications of tonsillectomy and adenoidectomy on children Psychoanal Stud Child, 7 126, 1952.

73 *Joslin E P Root H F White P Marbl A and Dasby C C* The treatment of diabetes mellitus 8th ed Lea and Febiger Philadelphia, 1947

74 *Kaartero R L* Lasten karvun aroosteleniaesta Lasten-tautien tutkimuosaation osaikaria 1966. 35

75 *Kaplan H I and Kaplan H S* Current theoretical concept in psychosomatic medicine Amer J Psychiat, 115 1091 1959

76 *Kasin E and Parker S* Schizophrenia nd diabetes Amer J Psychiat, 99 793 1943

77 *Katz P* Behaviour problems i juvenile diabetics Canad Med Ass J 76 783 1957

78 *Katz, S E* A catatonic syndrome associated with d abetes mellitus Arch Neurol and Psychiat 31 880, 1934

79 *Kennedy W B* Psychologic problems of the young diabetic Diabetes 4: 207 1955
80 Kessler J W Psychopathology of childhood. 2nd ed. Prentice Hall, Englewood Cliffs 1966.
81 *Knowles, H C Jr Guest, G M Lampe R M Kessler M and Skillman T G* The course of juvenile diabetes treated with unmeasured diet. Diabetes, 14 239 1965.
82 Korsch B M Psychological principles in pediatric practice the pediatrician and the sick child Adv Pediat, 11: 10 1958
83 *Kubany A J Danowski, T S and Moses, C* The personality and intelligence of diabetics Diabetes, 5 462, 1956
84 Kubie, L S The fallacious misuse of the concept of sublimation Psychoanal Quart, 31 73 1962
85 Langford, W S Physical illness and convalescence their meaning to the child J Pediat, 33 242, 1948
86 Langford W S Child in pediatric hospital adaptation to illness and hospitalization Amer J Orthopsychiat 31 667 1961
87 Larsson Y The organization and function of clinic for juvenile diabetes Acta Pediat Scand Supp 135 157 1962
88 Larsson, Y *and Sterky G* Long term prognosis in juvenile diabetes mellitus Acta Pediat Scand, Supp 130 1962
89 Lichtenstein A Diet in diabetes in childhood Adv Pediat 4 1 1949
90 *Loughlin W C and Mosenthal H O* Study of the personalities of children with diabetes Amer J Dis Child, 68 13 1944
91 *Mac Keith R* The adolescent who has handicap Med World, April 1964 296
92 *Kemer P* Suicide in adolescence Psychoanal Rev 41 48, 1954
93 *Mc Gavin A P Schultz E Peden C W and Bowen B D* The physical growth the degree of intelligence and the personality adjustment of group of diabetic children New Eng J Med, 223 119 1940
94 Menninger W C The interrelationship of mental disorders and diabetes mellitus J Ment Sci, 81 332, 1935
95 *Menninger W C* Psychological factors in etiology of diabetes J nerv Ment Dis 81 1 1935
96 Menninger K The vital balance The Viking Press New York 1964
97 *Meyer A Bollmeier L N and Alexander F* Correlations between emotions and carbohydrate metabolism in two cases of diabetes mellitus Psychosom Med 7 335 194.
98 *Mohr and Rowe* quoted by Menninger (94)
99 *Murphy I A* Emotional factors the patient with diabetes mellitus Bull Menninger Clin, 12 187 1948
100. *Mosteller F and Bush R R* Selected quantitative techniques Handbook of social psychology *Ed.* by Lindzey Addison-Wesley Cambridge, I, 1954.
101 *Nelson W E* Textbook of pediatrics. 8th ed W B Saunders Co, Philadelphia, 1964
102. Nielsen, C H Emotional and psychic factors in disease. JAMA, 89 1020 1927
103 *Nilsson S E* Genetic and constitutional aspects of diabetes mellitus. Acta Med Scand, Supp 375, 1962.
104 *Owens L B and Rackow S S* Prognosis in diabetic coma. basic importance of mental state. Amer J Med Sci, 198 252, 1939
105 *Palmer R W* The diabetic personality J Indiana Med Ass, 51 1399 1958.
106 *Peck, F F Sr and Peck, F P J* Tautologous diabetic coma — behavioural syndrome. Diabetes, 5 44 1956
107 *Pelkonen T Ela, O Harvonen L and Välimäki I* Physical working capacity of normal and diabetic children Ann Paed Fenn, 11 25 1965
108 *Pike H V* Significance of diabetes mellitus in mental disorder JAMA, 76 1571 1921
109 *Prugh D G Staub E M Sands H H Kirschbaum R M and Lenihan E A* Study of emotional reactions of children and families to hospitalization and illness Amer J Orthopsychiat, 23 70, 1953
110 *Rantakallio Leena* Diabetesnäytteiden kliininen tulkinta... Menetelmä [illegible] Tampereen Yliopiston Toimitteita, 1967
111 Rashkis, E H Child understanding of health Arch Gen Psychiat, 12 10, 1965.
112 *Roychaudhury A K* A case of diabetes mellitus Psychosom Med, 20 35 1958
113 *Reed J A* Diabetes and head injury case in court Diabetes, 4 377 1955
114 *Rosen H and Lidz, T* Emotional factors in the precipitation of recurrent diabetic acidosis Psychosom Med, 11 211 1949
115 *Rosenzweig, S Fleming, E E and Rosenzweig, L* The children form of the Rosenzweig Picture-Frustration Study J Psychol, 26 141 1948
116 *Sandler J and Joffe W G* Notes on childhood depression Int J Psycho Anal, 46 88, 1965
117 *Savage C H* quoted by Slawson et al (124)
118 *Schiff L J* Emotional problems of diabetic children and their parents. Psychosom 5 362, 1964
119 *Schless, G L and Lawrence Schless R* Recurrent episodes of diabetic acidosis precipitated by emotional stress Diabetes, 13 419 1964.
120 *Senn M J* Emotional aspects of convalescence. Child 10 24 1945

39 *Etzwiler D D and S net L A* Juvenile diabetes and it management family social nd academic implications. JAMA, 181: 304 1962.

40 *F gel G L* Homeostasis, beha ioral adjustment and the concep of health and disease. Mid-century Psychiat Ed. by Grinker Charles C Thomas, Springf: d 1953

41 *L gleson G* Diabetes mellitus. Nordisk laerobog I paediatri 5th ed Munksgaard Copenhagen, 1962

42. *alstein E I and Judas I* J venile diabetes and its psychiat implications Am J Orthopsychiat 25 330 1955

43 *F nch S M and Hess J* Ulcerati coliti children Am J P ychiat, 118 819 1962

44 *Fischer A E and Dolger H* Behavior and psychological problems of young diabetic patients. Arch Int Med, 78 711 1946.

45 *Fischer A E* Factors responsible for emotional disturbance in diabetic children. Nervous Child 7 78 1948.

46. *Friedman S B Mason J W and Hamburg D A* Urinary 1 -hydrocorticosteroid leve.s in parents of children with neoplastic disease Psychosom Med 25 364 1963

47 *F eud A* Role of bodily illness in mental life of children. Psychoanal Stud Child, 7 69 1952.

48 *Gamstorp I Shelburne S A J Engleson G Redondo D and Traisman H S* Peripheral neuropathy n j venile diabetes. Diabetes 15 411 1966

49 *Cetis H* The psychological aspects of diabetes Charles C Thomas Springfield, 1964

50 *Gendel B R nd Be jamin J E* Psychogenic factors in the etiology of diabetes New England J Med 234 556 1946

51 *Goldner M C* Stress corticoids and diabetes Diabetes 7 410 1958

52 *Goodman J I Schwartz F D and Frankel L* Group therapy of obese diabetic patients Diabetes, 2 280 1953

53 *Greenberg A and Blau J L* Social aspects of diabetes mellitus Diabetes 2 272 1953

54 *Hallgren B* Enuresis I A study w th reference to the morbidity ss and symptomatology Acta Psych Neurol Scand 31 379 1956

55 *Harris M M* Metabolic considera ions regard psychoses Arch Neur Psychiat 31 881 1934

56 *Helsi gin Ka pu ki* *tilastotoimisto* Sos aal tilasto 1965

57 *Hernberg C A and Heikel P E* The skeletal age in diabetic ch ldren Acta Paediat Scand 40 486, 1951

58 *Herskowitz H* A psychiatrist s view of diabetes mell tus Am Dietetic Ass J 12 40 1936

59 *Hinkle L E J Evans F M and Wolf S* Studies on diabetes mellitus. Psychosom Med, 13: 160, 1951

60 *Hinkle L E J d Wolf S* The 'fect of stressful life situations on the concentration of blood glucose in diabetic and nondiabet.c humans. Diabetes, 1 383 1952.

61 *H nkle L E J and Wolf S* A summary of experimental evidence relating life stress to diabetes mellitus. J Mt Sinai Hosp 19 537 1952.

62. *H nkle L E J and Wolf S* Importance of li stress in course and management of diabetes mellitus. AMA 148 513 1952.

63 *Hinkle L E J* The doctor patient relationship in the management of diabet.c patients and their emotional prob.ems New York J Med 53 1943 1953

64 *Hinkle L E J* The influence of the patient behaviour and his reaction to his lif tuation upon the course of diabetes. Diabetes, 5 406, 1956.

65 *Hinkle L E J Fischer A K owles H C J and Stunkard A J* Role of environment and personality i management of the difficult patient with diabetes mellitus. Diabetes, 8 371 1959

66 *Hinkle J E J* Customs, emotions and behaviour the dietary treatment of diabetes J Amer Diet Ass, 41 341 1962

67 *Holtzman W H* Holtzman Inkblot Technique. Mc Graw Hill Co. 1967

68 *Holtzman W H* Holtzman Inkb.ot Technique. Draft Copy 1966.

69 *Holtzman W H* Cross cultural research on personality development Human Devel 8 65 1965

70 *Holcomb B* The responsibilities of the diabetic physician. Diabetes 3 328 1954

71 *Jacobson E* Progressive relaxation. 2nd ed The University of Chicago Press Chicago, 1939

72 *J ssner L Blom G and Waldfogel S* Emotiona implications of tonsillectomy and adenoidectomy on children. Psychoanal Stud Child, 7 126, 1952

73 *Joslin E P Root H F White P Marble A and Danby C C* The treatment of diabetes mellitus 8th ed Lea and Febiger Philadelphia, 1947

74 *Kantero R L* Lasten kasvun arvosteleminesta Lasten tien tutkimussuation uosikirja 1966 35

75 *Kaplan H I and Kaplan H S* Current theoret cal concept i psychosomatic medicine Amer J Psychiat 115 1091 1959

76 *Kasin E and Parker S* Schizophrenia and diabete Amer J Psychiat 99 793 1943

77 *Katz P* Behaviour problems in juvenile diabetics Canad Med Ass J 76 783 1957

78 *Katz, S E* A catatonic syndrome associated with diabetes mellitus Arch Neurol and Psychia 31 880 1934

Appendixes

Str ctuded interview with the
pa nt

A The parent's immediate reaction to the illness of the child.

1 Could you tell me what kind of feelings or thoughts you had when you first got to know that your child had diabetes?
2 Did you cry? For how long?
3 Could you sleep? How many sleepless/almost sleepless nights did you have?
4 For how long did those first feelings and thoughts last? As time went on, did they change? If they changed, what kind of feelings and thoughts have on now about your child's illness?

B The coping processes

1 Now when your son/daughter has been sick for ——— years, what do you now think about his/her illness?
2 The diet and the insulin injections are both part of the daily care of the diabetic. Which one is more difficult for you?
3 Could you describe your sons/daughter morning schedule What do you speak about in the mornings?
4 How does your son/daughter react to the diet?
How does his/her diet differ from that of the other members of the family
How often does your child ask for sweets
How often do you indulge him
5 How does your son/daughter react to the insulin injections? Who gives the injections? Does your child ever do t himself?
6 How long did take before you became skilled in giving the injections
7 How long did it take before you got used to our child diet?
8 What do you do if the urinalysis reveals acids in your child urine?
9 Do you peak about your child illness t home What do you say about it? How often Do you speak about it with friends and relatives
10 Do your child s friends know about his/her diabetes? How do they react to t?
11 Do your child's teachers know about his/her diabetes? Who informed them? In what way? How did they react to it?

C The child

1 Has your child changed during his/her illness? In what way?
2 Could you tell me what kind of child he/she was before the diabetes? What kind of a child i he/she now?
3 Does your son/daughter look sad, depressed or unhappy most of the time/sometimes/never
4 I he/she interested in things or does he/she look bored or uninterested often? How often does he/she tell you interestedly what he/she has seen or done?
5 I he/she able to enjoy his/her life?
6 How does he/she react to frustrations?
7 How is his/her sleep?

2 Q tio a y to the te che

1 I — — — — — — — — level of
child name
achievement higher/the same/lower than the average level if his/her class?
2 Are his/her achievements more even/the same/more changing than the average of the class?
3 What are his/her best subjects?
4 What are his/her weakest subjects?
5 Compared with his/her classmates ,is he/she interested in things/bored and uninterested?
6 What things interest him/her?
7 Does he/she seem t take the school positively/indifferently/negatively?
8 How does he/she react to frustrations?
9 How is his/her relationship with the teachers?
10 How is his/her relationship with peers.
11 Could you tell me anything else which could have meaning when his/her scholastic achievement is evaluated.

121 *Sheppe W M and Sheppe W M J* The psychogenic problems of the young diabetic patient W Virginia Med J 50 65 1954

122. *Shirley H F and Greer I M* Environmental and personality problems in the treatment of diabetic children J Pediat 16: 775 1940

123 *Simon N H and Mirsky S* The roles of emotional stress and diet in the etiology of diabetes mellitus. Quart Bull Northwest Univ Med School 27 126 1953

124 *Slawson P Fl W R and Koller E J* Psychological factors associated with the onset of diabetes mellitus JAMA 185 166 1963

125 *Smith J A and Brown W T* Psychiatric effects of diabetes occurring late in lif Dis Nerv Syst 12 278 1951

126 *Sturek S A.* Comments on psychopathology of children with somatic illness. Amer J Psychiat 107 844 1951

127 *Starr P H* Psychosomatic considerations of diabetes in childhood J Nerv Ment Dis, 121 493 1955

128. *St arn S* Some emotional aspects of the treatment of diabetes mellitus and the role of the physician. New Eng J Med 249 471 1953

129 *Stearns S* Self-destructive beha iour in young patients with diabetes mellitus. Diabetes, 8. 379 1959

130 *Stenback A* Headache and lif stress. Acta Psychiat Neurol Scand Supp 92 1954

131 *Stephens J W and Marble A* Place and value of summer camps in management of j venile diabetes Amer J Dis Chil 82. 259 1951

132. *Sterky G* Diabetic schoolchildren Acta Pediat Scand Supp 144 1963

133 *Sterky G* Physical work capacity i diabetic schoolchildren Acta Pediat Scand, 52. 1 1963

134 *Swift C R and Seidman F L* Adjustment problems of juvenile diabetes J Amer Acad Child Psychiat 3 500 1964

135 *Swift C R. Seidman F and Stein H* Adjustment problems in juvenile diabetes. Psychosom Med 29 555 1967

136. *Soderl g B* Some re ections on ju enile diabetes and its treatment. Acta Pediat Scand, Supp 146 133 1963

137 *Tabala A* Rosenzweigin kuvafrustratiotesti. Suomen ja vastausten luokittelu. Jyvaskylan Kasvattajaopillisen Korkeakoulun Psykologian laitoksen julkaisuja, 6 1955

138 *Terman L M and Merrill M A* Measuring intelligence Houghton Mifflin, New York, 1937

139 *Thom on V* Studies of trauma and carbohydrate metabolism with specil reference to the existence of traumatic diabetes. Acta Med Scand, Supp 91 1938.

140 *Tisza V B* Management of the parents of the chronically ll child. Amer J Orthopsychiat 32: 53 1962.

141 *Tolstoi E.* The objectives of modern diabetic care. Psychosom Med, 10 29 1948

142. *Toolan J* Depression in children and adolescents Amer J Orthopsychiat 32. 404 1962.

143 *Treuti g T F* The ro'e of emotional factors in the etiology and course of diabetes mellitus. Amer J Med Sci 244 131 1962

144 Trowbridge R E Sociomedical aspects of d abetes mellitus. Lancet 2: 893 1953

145 *Wagner R White P and Bogen J K* Diabetic dwarfism Am J Dis Child, 49 243 1959

146. *Weil W B and Ack, M* School achievement in j venile diabetes mellitus Diabetes 13 303 1964

147 *Werkman S L* The psychiatric diagnostic interview with children Amer J Orthopsychiat 35 764 1965.

148 *W nicott D W* The depressive position in normal emotional development Collected papers. Tavistock London 1958

149 *Wolff H G* Brain and diabetes Diabetes 8 358, 1959

Appendixes

St tuded interview with th par nt

A The parent's immediate reaction to the illness of the child

1 Could you tell me what kind of feelings or thoughts you had when you first got to know that your child had diabetes?
2 Did you cry For how long?
3 Could you sleep? How many sleepless/almost sleepless nights did you have?
4 For how long did those first feelings and thoughts last As time went on, did they change? If they changed, what kind of feelings and thoughts has you now about your child's illness

B The coping processes

1 Now when your son/daughter has been sick for ——— years what do you now think about his/her illness?
2 The diet and the insulin injections are both part of the daily care of the diabetic. Which one is more difficult for you
3 Could you describe your sons/daughter' morning schedule What do you speak about in the mornings?
4 How does your son/daughter react to the diet?
How does his/her diet differ from that of the other members of the family
How often does your child ask for sweets? How often do you indulge him
5 How does your son/daughter react to the insulin injections Who gives the injections Does your child ever do t himself?
6 How long did take before you became skilled in giving the injections
How long did take before you got used to your child' diet?
8 What do you do if the urinalysis reveals acids in our child' urine?
9 Do ou speak about you child' illness at home? What do you say about it? How often Do you speak about it with friends and relatives?
10 Do your child's friends know about his/her diabetes? How do they react to it?
11 Do your child's teachers know about his/her diabetes? Who informed them? In what way? How did they react to it?

C The child

1 Has your child changed during his/her illness? In what way?
2 Could you tell me what kind of child he/she was before the diabetes? What kind of a child is he/she now?
3 Does your son/daughter look sad, depressed or unhappy most of the time/sometimes/never
4 Is he/she interested in things or does he/she look bored or uninterested often? How often does he/she tell you interestedly what he/she has seen or done?
5 Is he/she able to enjoy his/her lif ?
6 How does he/she react to frustrations?
7 How is his/her sleep?

2 Qu tionary to the teache

1 Is — — — — — — — — — s level of child' name achievement higher/the same/lower than the average level if his/her class?
2 Are his/her achievements more even/the same/more changing than the average of the class?
3 What are his/her best subjects?
4 What are his/her weakest subjects?
5 Compared with his/her classmates is he/she interested in things/bored and uninterested?
6 What things interest him/her?
7 Does he/she seem to take the school positively/indifferently/negatively?
8 How does he/she react to frustrations?
9 How is his/her elationship with the teachers?
10 How is his/her relationship with peers.
11 Could you tell me anything else which could have meaning when his/her scholastic ach'evement is evaluated.

Some drawings of the diabetic children



Figure 6 *Drawing of a boy 13 yrs belonging to the P group This drawing was made on the ward and makes an artificially gay impression*

Figure 7 *Drawing of the same boy as Fig 6 Made on the same day during a psychiatric interview It makes an unhappy and empty expression*



Figure 8 *Drawing of a girl 9 yrs belonging to the P group The Christmas tree was placed far in the left hand corner of the paper There are decorations only on one side of the tree*



Figure 9 *Drawing of a boy 11 yrs belonging to the P group An injection is given to a patient*

Figure 10. *Drawing of a girl 9 yrs belonging t the GF group Both the female figures are well drawn The unproportionally tall girl in the centre was stated by her to be dwarf girl She has big, sad eyes and short arms The story told by the girl is as follows On the other side f the forest there is the house of a witch The witch is looking through her window A dwarf girl tands n her own yard beautifully dressed There is path from the witch's house to the dwarf house along that path the witch sneaks in the nights*

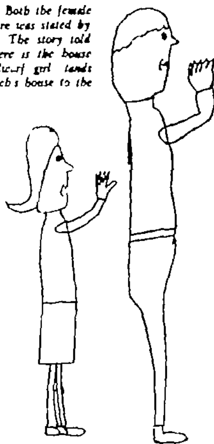


Figure 11 *Drawing of boy 11 yrs belonging t the P group Both the male figure (left) and the female figure (right) are drawn in profile They make somewhat mpty and lonely expression Y t the stories told by the boy indicat at least d sire for a companion hip*

The male f g This is like a boy saying hello t hi fried

The femal f gure "Thi looks mor like a lat blinking girl

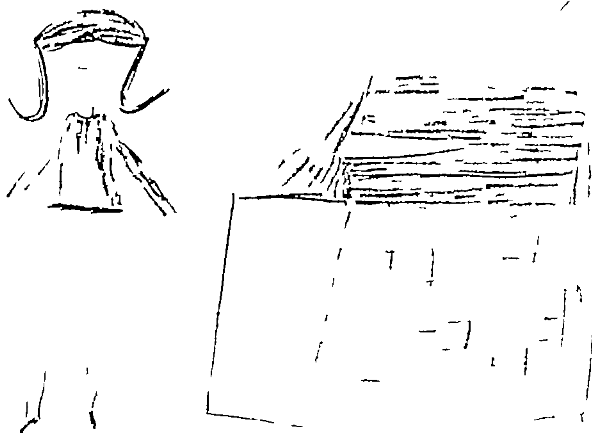


Figure 12 *Drawing of a girl 6 yrs belonging to the GF group Better than average drawing skill The most striking feature is the tallness of the girl compared with the house*

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

134. Möller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw kr 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw kr 25.— 1962
137. Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw kr 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen. 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wass-Hückert, Ole and Danner, Mirta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr. 25.— 1963
147. Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children, Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr. 20.— 1963
149. Valaes, Timos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw kr 25.— 1963
150. Mae, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum, Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics,* Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study. Sw kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr 25.— 1964
157. Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type 1 (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm. 1964. Edited by Y. Larsson. Sw kr 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw kr. 25.— 1965
161. Palsson, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw kr 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. kr 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw kr. 30.
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis. A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr 35.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children, a Longitudinal Study. Sw. kr 25.— 1966
169. Dahl, Mardi, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chevrant.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hämäläinen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967. Sw. kr 35.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw kr 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using a Passive Haemagglutination Technique. Sw. kr 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Elsa, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw kr 30.— 1969
188. Meeuwisse, Gunnar W., and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw kr 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 25.— 1969
191. Kaivikko, Antti, Cardiovascular Responses of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Groups at Risk in Low Birth Weight Infants and Perinatal Mortality. Sw. kr 30.— 1969
194. Kuusisto, Antti, Studies on the Serum Binding of Vitamin B₁₂ in the New[...] Infant. Sw kr 30.— 1969
195. Thom, Inr[...] al Symptoms in the Newborn. Sw. kr. 15.— 1969
196. Raskerr[...] and Psychological Factors Influencing Hosp[...] ltress with Special Reference to Mental Dwo[...] Symptoms. Sw kr. 25.— 1969
197. S[...] as Infections in Paediatric Surgical U[...]
8. [...] ping Pro[...] in Childhood Diabetes.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 197 1969

PSEUDOMONAS INFECTIONS IN A PAEDIATRIC SURGICAL UNIT

BY RITVA SUNILA

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden ithout charge

134. Möller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet,* June 30, 1962. Sw kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw kr 25.— 1962
137 Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review Sw. kr 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw kr 25.— 1962
139 Westin, Björn, Nyberg, Russ, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen. 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141 Wass-Häckert, Ole and Desser Mirta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study Sw. kr 25.— 1963
142. Sterner Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study Sw. kr 25.— 1963
144. Sterky Göran, Diabetic Schoolchildren. Sw kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1962.* Sw. kr. 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply Sw. kr 20.— 1963
149. Valaes, Tinos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr 25.— 1963
150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organisation of the X International Congress of Paediatrics,* Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr 15.— 1963
152. Hjern, Bo and Nylander, Ingvar Acute Head Injuries in Children Traumatology Therapy and Prognosis. Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism i Newborns. A Clinical and Cytogenetic Study. Sw kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr 25.— 1964
157 Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress,* Stockholm. 1964. Edited by Y. Larsson. Sw kr 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr 25.— 1965
161. Palmqvist, T and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw kr 20.— 1965
162. Landmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger Margareta, Studies on Immunization with and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Bronchiectasis. A Review of 187 Cases in up Pulmonary Function Studies in 58. Sw. kr. 20.—
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile toid Arthritis. Analysis of 544 Cases. Sw kr. 15.— 1.
167 Iversen, Torben, Leukaemia in Infancy and rial of 570 Danish Cases. Sw. kr 30.— 1966
168. Trojaborg, W Focal Spike Discharges in C nal Study Sw. kr 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the in Children. Sw kr 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr
171. Olding, Lars, Bacterial Infection in Cases of morphological and bacteriological study based on Sw kr 20.— 1966
172. *Festschrift in Memory of Constantin Choremis.* Sw. kr.
173. Walsh, S. Zoe, The Esophageal Electrocardiogram First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of clinical study before and after operation to haemodynamic function. Sw. kr. 25.— 1967
175. Hämäläinen, Pentti, Vectorcardiographic Studies in fants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial V Sw. kr. 20.— 1967
177 *Proceedings of the Fifteenth Northern Pediatri* C 1967 Sw. kr. 15.— 1967
178. Sjögren, Iréne, Echoencephalography in Paediatric Special Regard to Measurement of the kr 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulat* by Göran Wallgren. Sw kr 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the An sponse to *E. Coli* O-Antigens in Infants and Chi Urinary Tract Infection, Using Passive Technique. Sw kr. 20.— 1968
181. Koch, Günter Lung Function and Acid-Base Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A and Clinical Study Sw. kr. 25.— 1968
183. Robertson, Alex F and Sprecher, Howard, A Review Placental Lipid Metabolism and Transport. Sw. kr.
184. Robertson, Bengt, The intrapulmonary arterial pat infancy and in transposition of the great arteries. 1968
185. Andersen, Elsa, Skeletal Maturation of in Relation to Height, Sexual Development, tions. Sw kr 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi of the Literature and Report of Nine Cases. Sw kr.
187 Karlberg, Petter, *et al.,* The Development of Ch dish Urban Community. A Prospective Sw. kr. 30.— 1969
188. Meeuwisse, Gunnar W., and Melin, Kerstin, S Galactose Malabsorption. A Clinical Study of 6 Genetic Study Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation Monoxide in Full-Term Newborn Infants. Sw kr.
190. Hörnblad, P Yngve, Experimental Studies on Cl Ductus Arteriosus Utilizing Whole-Body F 1969
191 Kelvikko, Antti, Cardiovascular Response of the to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory in Children. Sw. kr 30.— 1969
193. Rantakallio, Paula, Groups at Risk in Low Birth Wei and Perinatal Mortality. Sw kr. 30.— 1969
194. Kamante, Antti, Studies on the Serum Binding of V in the Newborn Human Infant. Sw kr 30.— 1969
195. Thora, Ingrid, Cerebral Symptoms in the Newborn. Sw 1969
196. Rasberg, Georg, Social and Psychological Factors Hospital Admission of Children ith Special Reference Disorders and Functional Symptoms. Sw kr. 20.— 19
197 Sandle, Ritva, Pseudomonas Infections in Paediatri Unit. Sw kr. 20.— 1969
198. Kasid, Maija-Liisa, The Coping Processes in Childh Sw. kr 30.— 1969

Price Swed. kr 30 —

ACTA PAEDIATRICA SCANDINAVICA
SUPPLEMENT No. 197 1969

From the Children Hospital, Helsinki University Central
Hospital, Helsinki, Finland

PSEUDOMONAS INFECTIONS IN A PAEDIATRIC SURGICAL UNIT

By
Ritva Sunila

HELSINKI 1969

ACTA PAEDIATRICA SCANDINAVICA
SUPPLEMENT No. 197 1969

From the Children's Hospital, Helsinki University Central
Hospital, Helsinki, Finland

PSEUDOMONAS INFECTIONS IN A PAEDIATRIC SURGICAL UNIT

By
Ritva Sunila

HELSINKI 1969

Printed in Finland by
Paperi ja P in tuot Ky Helsinki 1969

Acknowledgements

The subject of the present investigation was suggested to me by Professor Niilo Hallman, M.D. and his excellent advice and never failing interest in my work were a most encouraging support to me.

Dr. Paavo Makelä, M.D. has from the very beginning of my work given me all kinds of help, advice and friendly criticism. Professor Ilari Rantasalo, M.D. and Professor Ossi Pettay, M.D. have spent time in reading the manuscript and they have given me valuable advice and criticism.

Professor Lars Hjelt, M.D. has kindly given me the results of autopsies and histological examinations. Dr Juhani Rapola, M.D. examined the specimens for specific histological changes.

Mrs. Irja Kohonen, R.N. was a skillful and experienced assistant in the laboratory work. The mathematical analysis was carried out by Mr. Sampo Salovaara, Techn. D. Mr E. Liukkela drew the illustrations and Miss Elvi Kaukokallio translated the manuscript into English with great skill and experience.

I wish to express my warm thanks to them all.

I am also very grateful to the staff of the Children's Hospital of the University of Helsinki for pleasant co-operation and assistance during the study.

The study was financially aided by the Foundation for Paediatric Research in Finland.

Rovaniemi, January 1969

Ritva Similä

Printed in Finland by
Paperi- j Painotuote ky Helsinki 1969

Contents

Contents

Introduction

Over two decades ago there was observed an *increasing occurrence of outbreaks of hospital* infection due to *Staphylococcus aureus.* At the same time an increase was seen in infectious diseases caused by gram-negative bacilli (7 63, 73, 150, 180) This increase probably occurred to marked degree on the base f hospital infection, in the etiology of which the gram-negative bacilli have in recent years ttained equal significance ith the staphylococcus or even ha replaced it as the chief causati e gent (7 25, 60, 84 132, 160).

Among these gram-negative bacilli the most notorious cause f hospital infection is *Pseudomonas aeruginosa.* Previously it ery rarely was the causati agent, but during approximately the past 20 years ery large number of studies have been published on infections and hospital epidemics due to *Pseudomonas* (10, 15, 53 55 56, 61 72, 84 118, 160 161 180)

Cases of infection ascribable to gram-negativ bacilli, particularly to *Pseudomonas,* were observed to h e increased in the Children Hospital of the Helsinki University Central Hosp tal, especially in its surgical unit for chil dren under 2 years of ge and in the newborn ward (132). For this reason there was considered to be reason to undertake a study for clarification of the characteristics and significance of these *Pseudomonas* infections.

Introduction

Over two decades ago there was observed an increasing occurrence of outbreaks of hospital infection due to *Staphylococcus aureus*. At the same time an increase was seen in infectious diseases caused by gram-negative bacilli (7 63, 75, 150, 180) This increase probably occurred to a marked degree on the base of hospital infection, the etiology of which the gram-negative bacilli have in recent years attained equal significance with the staphylococcus or even have replaced it as the chief causative agent (7 25 60 84 152, 160).

Among these gram-negative bacilli the most notorious cause of hospital infection is *Pseudomonas aeruginosa* Previously it very rarely was the causative agent, but during approximately the past 20 years a very large number of studies have been published on infections and hospital epidemics due to *Pseudomonas* (10, 15 53, 55, 56, 61 72, 84 118, 160, 161 180)

Cases of infection ascribable to gram-negative bacilli, particularly to *Pseudomonas*, were observed to have increased in the Children Hospital of the Helsinki University Central Hospital especially in its surgical unit for children under 2 years of age and in the newborn ward (132). For this reason there was considered to be reason to undertake a study for clarification of the characteristics and significance of these *Pseudomonas* infections.

Review of the Literature

Bacteriological Properties of *Pseudomonas aeruginosa*

Pseudomonas is a large genus of bacteria containing numerous water and soil organisms present everywhere in nature and usually apathogenic to man The only species actually pathogenic to humans is *Pseudomonas aeruginosa* which also occurs in nature in various humid environments, especially in sewage water (30 90 177)

Pseudomonas aeruginosa is a gram negative motile rod shaped bacterium It grows aerobically in all nutrient media readily forming the typical colony The *Pseudomonas* may produce haemolysins as well as a green pigment of two types the blue-green pyocyanine and the yellow green fluorescein It can usually be differentiated readily from other gram negative bacilli by biochemical reactions. The optimum temperature for the *Pseudomonas* is +37 C, but it can multiply at temperatures between +5 and +42 and is destroyed at +55 within 1 hour (177) An apathogenic member of the genus, *Pseudomonas fluorescens*, also produces fluorescein but does not grow at +42° or form pyocyanine (30 177)

The *Pseudomonas* produces an endotoxin which, like those of other gram negative bacilli is a lipopolysaccharide and which on injection into experimental animals gives rise to symptoms of shock (17? 177)

Serologically a number of types are recognizable on basis of both their flagellar and somatic antigens (30 54 99 177) as well as by means of pyocine, the bacteriocine produced by the bacterium (41) Groups possessing similar lytic properties can also be distinguished by means of bacteriophages (30 177)

Occurrence of *Pseudomonas aeruginosa* in Man

In the normal bacterial flora of the human skin and mucous membranes the *Pseudomonas* is conspicuously rare except in hospital populations. Numerous publications report only 1 to 3 % of the examined persons to be faecal carriers of the organism (17 18, 78, 90 93, 94 99), and its occurrence in the nose throat or skin is evidently still more infrequent (99)

In hospital environments, and especially during hospital epidemics, carriers of *Pseudomonas* have been found in considerably larger numbers (14 90 93, 99 118) In some investigations up to half of the patients have been carriers (116).

Likewise the *Pseudomonas* does not belong to the first bacterial flora of the skin and mucous membranes of the newborn infant (37 57 142, 119 165 173, 174) The reason probably is the rare occurrence of this organism in parturients vagina or faeces, the flora in which evidently forms the basis of a large part of the bacterial flora of the newborn (13, 35, 119 173)

In the studies published from maternity hospitals and newborn nurseries there is considerable variation in the incidence of infants colonized with *Pseudomonas*, apparently depending on the epidemic situation at the various times (18, 92, 116)

Factors Favouring *Pseudomonas* Colonization

The high incidence of *Pseudomonas* carriers in various hospital series speaks for the probability that some special circumstances in t[illegible]

hospital en ironment are f ourable to *Pseudomonas* colonization. Factors that promote spread of the organism are probably the massiveness of the infection disseminated by the grossly infected patient (97 99, 164 167), the use of arious items f equipment that are difficult to clean, such as anaesthesia apparatuses (71 152, 161), respirators (125) oxygen equipment (45) and nebulizers (45 110, 111 112, 146), the abundant moisture used in the care of newborn infants (69), and the poor action against *Pseudomonas* of the commonly used disinfectants (12, 95, 98 100, 120, 127).

Colonization-promoting factors may also be present in the hospital patients themselves. Generally it is difficult for a bacterium to gain foothold on skin or mucous membranes that already ha a bacterial flora (155, 147 177). This flora is lacking in the newborn, who usually acquires it during the first 1 to 5 days of lif (44 149, 163). On the other hand, the cutaneous and mucosal bacterial flora, usually f saprophytic nature sensiti to antibiotics, can be destroyed or t least reduced in number by the use of antibiotics, thus providing resistant bacteri good opportunity for colonization. It has been observed, in fact, th t during antibiotic therapy the pharyngeal flora readily changes in about 5—7 da to one consisting mainly f gram-negati e bacilli (52, 65, 105, 180).

The bacterial flora on the skin and mucous membranes f severely ill patients has also been found to be con erted to a flora f gram-negati bacilli within ery short time, presumably also without the action f antibiotics (154)

Factors Influencing Development of *Pseudomonas* Infection

The pathogenicity of *Pseudomonas* to man is in general low and onset of infection even in colonized person therefore requires the presence of some factor that impairs the defence mechanism of the body Thi- --- be rare indi idual weakne s f ntibody ation (78, 151), but there also ha e been encountered among hospital patients certain groups th t are especially susceptible to infections produced by *Pseudomonas*.

Newborn infants, prematures in particular ha e been observed to be sensitive to all infections by gram-negative bacilli (8, 15, 46, 60, 72, 75, 118, 121 150, 155) For the greater part this may be due to a clearly evident deficiency of immunoglobulins in prematures and other newborn (8, 68, 144) Antibodies to gram-negative bacilli are present mainly in the gamma-M fraction of immunoglobulins, which does not pass from mother to child but which the newborn rapidly begins to form already during the first week of life (5, 144), probably in response to growth of intestinal bacillary flora of maternal origin (8, 144). Possibly the child is partly protected against these maternal bacilli by antibodies received both in gamma-G-globulin via the placenta and in breastmilk (8, 82)

Other properties f the newborn infant may also increase its sensitivity to infection. The thin skin, short trachea and open umbilical blood essels offer infecti organisms ready access into the body (96) In premature babies the capacity of leucocytes to phagocytize *Pseudomonas* bacilli has been found to be definitely poorer than in the full-term newborn (35).

The frequently observed susceptibility of infants and also of older children to *Pseudomonas* infections (36 40 59 72, 75, 81 94 156) is doubtlessly likewise based on antibody deficiency It has been demonstrated that the content in serum of haemaggl tinating antibodies to *Pseudomonas* is quite low up to the third year of lif and that more marked rise is seen only in the sixth year of lif (81)

P tients with burn wounds have appeared to be especially sensit e to *Pseudomonas* infections (81 99 167). The protein-rich exudate from the burnt area seems to form a good nutrient bed for infection, and in the bsence of the normal protecti barrier of healthy skin the infection can penetrate into the deeper tissues (162, 177). Furthermore, the antibody level of the patient with burns is depressed, presumably because f loss of protein through the lesion (81).

Review of the Literature

Bacteriological Properties of *Pseudomonas aeruginosa*

Pseudomonas is a large genus of bacteria containing numerous water and soil organisms present everywhere in nature and usually apathogenic to man. The only species actually pathogenic to humans is *Pseudomonas aeruginosa* which also occurs in nature in various humid environments especially in sewage water (30 90 177)

Pseudomonas aeruginosa is a gram negative motile, rod-shaped bacterium. It grows aerobically in all nutrient media, readily forming the typical colony The *Pseudomonas* may produce haemolysins as well as a green pigment of two types the blue-green pyocyanine and the yellow green fluorescein. It can usually be differentiated readily from other gram negative bacilli by biochemical reactions. The optimum temperature for the *Pseudomonas* is +37 C, but it can multiply at temperatures between +5 and +42 and is destroyed at +55 within 1 hour (177) An apathogenic member of the genus, *Pseudomonas fluorescens* also produces fluorescein but does not grow at +42° or form pyocyanine (30 177)

The *Pseudomonas* produces an endotoxin which, like those of other gram negative bacilli, is a lipopolysaccharide and which on injection into experimental animals gi es rise to symptoms of shock (172, 177)

Serologically a number of types are recogniz able on basis of both their flagellar and somat ic antigens (30 51 99 177) as well as by means of pyocine, the bacteriocine produced by the bacterium (41) Groups possessing similar lytic properties can also be distinguished by means of bacteriophages (30 177)

Occurrence of *Pseudomonas aeruginosa* in Man

In the normal bacterial flora of the human skin and mucous membranes the *Pseudomonas* is conspicuously rare except in hospital popu lations. Numerous publications report only 1 to 3 % of the examined persons to be faecal car riers of the organism (17 18 78 90 93 94 99) and its occurrence in the nose throat or skin is evidently still more infrequent (99)

In hospital environments, and especially during hospital epidemics, carriers of *Pseudomonas* have been found in considerably larger numbers (11 90 93 99 118) In some investigations up to half of the patients have been carriers (116)

Likewise the *Pseudomonas* does not belong to the first bacterial flora of the skin and mucous membranes of the newborn infant (37 57 142, 149 163 173 174) The reason probably is the rare occurrence of this organism in parturients vagina or faeces, the flora in which evidently forms the basis of a large part of the bacterial flora of the newborn (13 35 119 173)

In the studies published from maternity hospitals and ne born nurseries there is con sid rable variation in the incidence of infants colonized with *Pseudomonas* apparently depend ing on the epid mic situati n at the various times (18, 92, 116)

Factors Favouring *Pseudomonas* Colonization

The high incidence of *Pse lon onas* carriers in various hospital series speak for the prob ability that some special circum tances in th

hospital environment are f ourable to *Pseudomonas* colonization. Factors that promote spread of the organism are probably the massiveness of the infection disseminated by the grossly infected patient (97 99 164 167) the use of arious items of equipment that are difficult to clean, such as anaesthesia pparatuses (71 152, 161) respirators (125) oxygen equipment (43) and nebulizers (45, 110, 111 112, 146) the abundant moisture sed in the care of newborn infants (69). and the poor action gainst *Pseudomonas* f the commonly used disinfectants (12, 95 98, 100, 120, 127)

Colonization-promoting factors may also be present in the hospital patients themsel es. Generally t is difficult for bacterium to gain foothold on skin or mucous membranes that already ha bacterial flora (156, 147 177). This flora is lacking in the newborn, who usually acquires it during the first 1 to 3 days of life (44 149 163) On the other hand, the cutaneous and mucosal bacterial flora, usually of saprophytic ture sensiti to antibiotics, can be destroyed or at least reduced in umber by the use of antibiotics, thus providing resistant bacteria good opportunity for colonization. It has been observed, in fact, that during antibiotic therapy the pharyngeal flora readily changes in bout 5–7 day to one consisting mainly of gram-negat bacilli (52, 63, 105, 180).

The bacterial flora on the skin and mucous membranes of severely ill patients has also been found to be converted to a flora of gram negative bacilli within a ery short time, presumably also w thout the action f antibiotics (154)

Factors Influencing Development of *Pseudomonas* Infection

The pathogenicity f *Pseudomonas* to man is in general low and onset of infection even in colonized person therefore requires the presence of some factor that impairs the defence mechanism of the body This may be rare individual weakness in a tibody formation (76, 151), but there also has been encountered among hospital patients certain groups that are especially susceptible to infections produced by *Pseudomonas*.

Newborn infants, praematures in particular has been observed to be sensit e to all infec tions by gram-negati e bacilli (8, 15, 46, 60 72, 75, 118, 121 150, 155). For the greater part this may be due t a clearly evident deficiency of immunoglobulins in praematures and other newborn (8 68, 144). Antibodies to gram-negative bacilli are present mainly in the gamma-M-fraction of immunoglobulins, which does not pass from mother to child but which the newborn rapidly begins to form already during the first week f lif (5, 144), probably in response to growth of intestinal bacillary flora of maternal origin (8, 144). Possibly the child is partly protected against these maternal bacilli by antibodies recei ed both in gamma-G-globulin via the placenta and in breastmilk (8, 62)

Other properties of the newborn infant may also increase its sensiti ty to infection. The thin skin, short trachea and open umbilical blood essels offer infecti e organisms ready access into the body (96) In praemature babies the capacity of leucocytes to phagocytise *Pseudomonas* bacilli has been found to be definitely poorer than in the full-term newborn (33).

The frequently observed susceptibility of in fants and also of older children to *Pseudomonas* infections (36, 40, 59, 72, 75, 81, 94 155) is doubtlessly likewise based on antibody deficiency It has been demonstrated that the content in serum f haemagglutinating antibodies to *Pseudomonas* is quite low up to the third year of life and that a more marked rise is seen only in the sixth year of life (81)

Patients with burn wounds ha e ppeared to be especially sensiti e to *Pseudomonas* infections (81 99 167). The protein-rich exudate from the burnt area seems to form a good nutrient bed for infection, and in the bsence f the normal protecti e barrier of healthy skin the infection can penetrate into the deepe tissues (162, 177) Furthermore the antibody level f the patient with burns is depressed, presumably because of loss of protein through the lesion (81).

Review of the Literature

Bacteriological Properties of *Pseudomonas aeruginosa*

Pseudomonas is a large genus of bacteria containing numerous water and soil organisms present everywhere in nature and usually apathogenic to man. The only species actually pathogenic to humans is *Pseudomonas aeruginosa* which also occurs in nature in various humid environments, especially in sewage water (30 90 177)

Pseudomonas aeruginosa is a gram negative motile rod shaped bacterium. It grows aerobically in all nutrient media, readily forming the typical colony The *Pseudomonas* may produce haemolysins as well as a green pigment of two types the blue-green pyocyanine and the yellow green fluorescein. It can usually be differentiated readily from other gram negative bacilli by biochemical reactions. The optimum temperature for the *Pseudomonas* is +37° C but it can multiply at temperatures between +5 and +42 and is destroyed at +55° within 1 hour (177) An apathogenic member of the genus, *Pseudomonas fluorescens* also produces fluorescein but does not grow at +42° or form pyocyanine (30 177)

The *Pseudomonas* produces an endotoxin which like those of other gram negative bacilli, is a lipopolysaccharide and which on injection into experimental animals gives rise to symptoms of shock (172, 177)

Serologically a number of types are recognizable on basis of both their flagellar and somatic antigens (30 54 99 177) as well as by means of pyocine, the bacteriocine produced by the bacterium (41) Groups possessing similar lytic properties can also be distinguished by means of bacteriophages (30 177)

Occurrence of *Pseudomonas aeruginosa* in Man

In the normal bacterial flora of the human skin and mucous membranes the *Pseudomonas* is conspicuously rare except in hospital populations. Numerous publications report only 1 to 3 % of the examined persons to be faecal carriers of the organism (17 18, 78, 90 93, 94 99), and its occurrence in the nose throat or skin is evidently still more infrequent (99)

In hospital environments, and especially during hospital epidemics, carriers of *Pseudomonas* have been found in considerably larger numbers (14 90 93 99 148) In some investigations up to half of the patients have been carriers (116)

Likewise the *Pseudomonas* does not belong to the first bacterial flora of the skin and mucous membranes of the newborn infant (37 57 142, 149 163, 173 174) The reason probably is the rare occurrence of this organism in parturients vagina or faeces, the flora in which evidently forms the basis of a large part of the bacterial flora of the newborn (13, 35 119 173)

In the studies published from maternity hospitals and newborn nurseries there is considerable variation in the incidence of infants colonized with *Pseudomonas* apparently depending on the epidemic situation at the various times (18 92, 116)

Factors Favouring *Pseudomonas* Colonization

The high incidence of *Pseudomonas* carriers in our hospital series speaks for the probability that some special circumstances in the

100 / (50 55, 77 155, 172). Endotoxin shock possibly associated with septicaemia greatly influences the prognosis. Mortality in *Pseudomonas* septicaemia among adults has been reported at about 80 / when endotoxin shock was present, and at 20 / in other cases (172)

Histologically the typical change in Pseudomonas infections is a diffuse acute vasculitis, with abundant bacteria on the vascular walls, and haemorrhages, thromboses and necroses in the adjacent tissues (55).

Epidemics Caused by *Pseudomonas*

In the non-hospital population the Pseudomonas is rarely the causative agent in primary infectious processes (55, 77 87 102, 129 177), and epidemics are also of rare occurrence except in hospitals. However there are reports of diarrhoea epidemics due to infected milk or well-water (17 143).

In hospitals, on the other hand, *Pseudomonas has been the cause of epidemics, some of which* have been quite large, and these hospital infections have increased considerably within the last two decades (19 50, 56. 55 55). They have been quite numerous in newborn and praematurе nurseries (10 21 22, 39 47 69 72, 89, 92, 94 115, 116 128, 152, 165, 167 178) and in urological and burns units (50, 81 99 106, 108, 109, 114 130, 167) They have also been reported from other units (17 18, 43, 127 158, 159, 167 176)

For the onset of hospital infection with *Pseudomonas* there are certain preconditions, which were brought out by Wahba in his investigation in 1965 (167) Using a combined pyocine and serological typing method he studied the *Pseudomonas* strains in different kinds of hospital wards Where the incidence of infection was low the isolated strains were often of various types presumably brought in by patients and the infections were to a great extent autogenous This situation he found in the eye, ear and surgical wards, whereas in the urological, burns and paediatric units a certain strain often was dominant for some length of time and an epidemic of clearly this type prevailed in the ward.

An essential factor in the onset of an epidemic appeared to be the number of infection-susceptible patients in the ward. When they were few in number the *Pseudomonas* spread slowly and the various cases were caused by different types of the micro-organism. When there were many patients of this kind, some given strain became predominant and was the cause of numerous cases of infection in the course of weeks or months.

Wahba summarized the situation by stating that whenever highly susceptible patients came in contact with heavy disseminators of the organism, cross-infection was common (167)

Routes of Transmission of *Pseudomonas* Infection

It is apparent that the *Pseudomonas* bacterium can spread in various ways, as by contact, by air or by way of contaminated hospital equipment (55, 60 175). The relative importance and share of these routes in the spread of the infection probably differ according to the hospital conditions and the type of patients.

Transmission by hands. A patient with burns, diarrhoea or urinary tract infection who is infected with *Pseudomonas* readily contaminates the hands of the nursing staff (54 99, 106). *Often the bedding and urine bottles of these* patients are also highly contaminated (54 99, 106 150) and handling them may probably also contaminate the hands.

Gram negative bacilli do not belong to the normal permanent bacterial flora of the skin and they disappear spontaneously (136, 177) However even this brief period may be sufficient for the organism to become transferred to another patient or to equipment. It has also been demonstrated that after massive contamination it is difficult to fully free the hands from the organism by washing and disinfectants, though its amount will be greatly decreased (100) Since *Pseudomonas* is able to survive and even to grow

Cases of urinary tract infection with *Pseudomonas* have been described in patients with indwelling catheter and in operated patients (55 106 108 130) Animal experiments have shown that obstruction or foreign bodies in the urinary tract predispose to infection even in the presence of a fully normal antibody level of the body (141)

The susceptibility to bacillary infections often seen in patients with leucaemia and aplastic anaemia and persons receiving radiotherapy or x ray treatment (15 19 25 56 75 166, 167 176) is held to be largely a result of lowering of the general resistance of cells and depression of antibody formation by irradiation as well as by antimetabolites and cortisone (24 67 115 177)

Patients with chronic pulmonary processes and fibrosis of the pancreas have been observed to be sensitive to *Pseudomonas* infection (42, 72 167 176) The basic disease in these cases probably lowers the resistance of the bronchial mucosa, rendering it easier for possible pathogenic pharyngeal bacteria to attack the bronchi (29 62, 86 91)

It is a generally accepted opinion that antibiotic therapy predisposes to *Pseudomonas* infections (15 175 180) The basis may be that colonization is facilitated by disappearance of the sensitive normal mucosal flora and that, at least in the newborn, antibody formation is weaker owing to disappearance of the innocent intestinal flora of maternal origin (8, 144 177) Experiments in vitro have also indicated that growth of some *Pseudomonas* strains is stimulated by tetracyclines or chloramphenicol (145)

Infections Due to *Pseudomonas*

The *Pseudomonas* may produce both localized infectious foci as well as systemic infection. The incubation time is 5–7 days (116 155) When the infectious agent directly attacks the meninges (77) or the trachea (125 159) incubation requires only 1–2 days.

Infections of the external auditory canal and the middle ear are typical *Pseudomonas* infections (55 123 165) However it is rarely encountered as the causative agent in acute otitis media, being more common in chronic processes in the ear (30 55 87 122, 155) It can cause infections of the eye of various kinds, from conjunctivitis to panophthalmitis (18, 30, 55) Burns and operation wounds may become infected (15 30 55 99 177) and likewise the umbilical stump of the newborn infant (92, 143, 155) Associated with *Pseudomonas* infections there are a great variety of skin symptoms, being evidently secondary signs of the septicaemia, and manifesting either as metastatic foci or toxic reactions (55)

The *Pseudomonas* has been found to give rise to respiratory tract infections of various kinds and degrees. Cases have been described of purulent rhinitis (113 155) bronchitis, pneumonia, abscess of the lungs and empyema (55, 143, 155) It has been found to cause localized infectious foci on the pharyngeal mucosa and in the parotid glands (39 55) as well as infections of the lower alimentary tract, diarrhoea of varying degree, and peritonitis (30, 54 55 94 143, 155) It has also been responsibl for urinary tract infections (30 55 177) and meningitis (30 55 77)

All of the above conditions may lead to septicaemia, to which the newborn infant in particular is susceptible (55 56 118 143) Septicaemia has been found to develop especially on the base of infected operation wounds, burns, urological operations and umbilical infection (55 81 143, 172) but it can also occur without a clearly evident primary focus (55) Septicaemia due to *Pseudomonas* like bacteraemia from other gram negative bacilli may be accompanied by endotoxin shock (172)

In the published series of *Pseudomonas* infections the recovery and mortality incidences have varied over a wide range They have doubtlessly been influenced by marked differences in the susceptibility to infection of the various patient groups as well as by fairly great differences in treatment. However mortality is almost without exception high in the more severe forms of disease, such as peritonitis meningitis and septicaemia with incidences ranging from 20 to nearly

100 % (50, 55, 77 155, 179). Endotoxin shock possibly associated with septicaemia greatly influences the prognosis. Mortality in *Pseudomonas* septicaemia among adults has been reported at about 80 % when endotoxin shock was present, and t 20 % in other cases (172).

Histologically the typical change in *Pseudomonas* infections is diffuse acute vasculitis, with abundant bacteria on the vascular walls, and haemorrhages, thromboses and necroses in the adjacent tissues (55)

Epidemics Caused by *Pseudomonas*

In the non-hospital population the *Pseudomonas* is rarely the causative agent in primary infectious processes (55, 77 87 102, 129 177), and epidemics are also of rare occurrence except in hospitals. However, there are reports of diarrhoea epidemics due to infected milk or well-w ter (47 143)

In hospitals, on the other hand, *Pseudomonas* has been the cause of epidemics, some of which ha e been quite large, and these hospital infec tions ha e increased considerably within the last two decades (19, 50, 56, 55, 55) They have been quite numerous in newborn and praematune nurseries (10 21 22, 39, 47 69 72, 89 92, 94 115, 116, 128, 152, 165, 167 178) and in urological and burns units (50, 81 99 106, 108, 109 114 150, 167). They ha also been reported from other units (17 18, 45, 127 148, 159, 167 176).

For the onset of a hospital infection with *Pseudomonas* there are certain preconditions, which were brought out by Wahba in his investigation in 1965 (167) Using combined pyocine and serological typing method he studied the *Pseudomonas* strains in different kinds of hospital w rds Where the incidence of infection was low the isolated strains were often f various types presumabl brought in by patients and the infections were to great extent autogenic. This situation he found in the eye, ear and surgical wards, whereas in the urological, burns and paediatric units a certain strain often was dominant for some length f time and an epidemic of clearly this type prevailed in the ward.

An essential factor in the onset f an epidemic ppeared to be the number of infection-susceptible patients in the ward. When they were few in number the *Pseudomonas* spread slowly and the arious cases were caused by different types of the micro-organism. When there were many patients of this kind, some given strain became predominant and was the cause of numerous cases of infection in the course of weeks or months.

Wahba summarized the situ tion by stating that whenever highly susceptible patients came in contact with heavy disseminators of the organism, cross-infection was common (167)

Routes of Transmission of *Pseudomonas* Infection

It is pparent that the *Pseudomonas* bacterium can spread in arious ways, as by contact, by air or by way of contaminated hospital equipment (55 60, 175). The relati importance and share f these routes in the spread of the infection probably differ according to the hospital conditions and the type f patients.

Transmission by hands. A patient with burns, diarrhoea or urinary tract infection who is infected with *Pseudomonas* readily contaminates the hands of the nursing staff (54 99 106). Often the bedding and urine bottles of these patients are also highly contaminated (54 99 106, 150) and handling them may probably also contaminate the hands.

Gram-negati bacilli do not belong to the normal permanent bacterial flora of the skin and they disappear spontaneously (136, 17"). However, even this brief period may be sufficient for the organism to become transferred to another patient or to equipment. It has also been demonstrated that after massi contamination it is difficult to fully free the hands from the organism by washing and disinfectants, though its amount will be greatly decreased (100). Since *Pseudomonas* is able to survive and even to grow

Cases of urinary tract infection with *Pseudomonas* have been described in patients with in dwelling catheter and in operated patients (55 106 108 130) Animal experiments have shown that obstruction or foreign bodies in the urinary tract predispose to infection even in the presence of a fully normal antibody level of the body (111)

The susceptibility to bacillary infections often seen in patients with leucaemia and aplastic anaemia and persons receiving radiotherapy or x ray treatment (15 19 25 56, 75 166 167 176) is held to be largely a result of lowering of the general resistance of cells and depression of antibody formation by irradiation as well as by antimetabolites and cortisone (24 67 115 177)

Patients with chronic pulmonary processes and fibrosis of the pancreas have been observed to be sensitive to *Pseudomonas* infection (42, 72, 167 176) The basic disease in these cases probably lowers the resistance of the bronchial mucosa, rendering it easier for possible pathogenic pharyngeal bacteria to attack the bronchi (29 62 86 91)

It is a generally accepted opinion that antibiotic therapy predisposes to *Pseudomonas* infections (15 175 180) The basis may be that colonization is facilitated by disappearance of the sensitive normal mucosal flora and that, at least in the newborn, antibody formation is weaker owing to disappearance of the innocent intestinal flora of maternal origin (8 144 177) Experiments in vitro have also indicated that growth of some *Pseudomonas* strains is stimulated by tetracyclines or chloramphenicol (145)

Infections Due to *Pseudomonas*

The *Pseudomonas* may produce both localized infectious foci as well as systemic infection The incubation time is 5–7 days (116, 155) When the infectious agent directly attacks the meninges (77) or the trachea (125 159) incubation requires only 1–2 days.

Infections of the external auditory canal and the middle ear are typical *Pseudomonas* infections (55 125 165) However it is rarely encountered as the causative agent in acute otitis media being more common in chronic processes in the ear (30 55 87 122, 155) It can cause infections of the eye of various kinds, from conjunctivitis to panophthalmitis (18, 30, 55) Burns and operation wounds may become infected (15 30 55 99 177) and likewise the umbilical stump of the n wborn infant (92, 143, 155) Associated with *Pseudomonas* infections there are a great variety of skin symptoms, being evidently secondary signs of the septicaemia and manifesting either as metastatic foci or toxic reactions (55)

The *Pseudomonas* has been found to give rise to respiratory tract infections of various kinds and degrees. Cases have been described of purulent rhinitis (113, 155) bronchitis, pneumonia, abscess of the lungs and empyema (55, 143, 155). It has been found to cause localized infectious foci on the pharyngeal mucosa and in the parotid glands (39 55) as well as infections of the lower alimentary tract, diarrhoea of varying degree, and peritonitis (30 54 55 94 143, 155) It has also been responsible for urinary tract infections (30 55 177) and meningitis (30, 55, 77)

All of the above conditions may lead to septicaemia to which the newborn infant in particular is susceptible (55, 56 118 143) Septicaemia has been found to develop especially on the base of infected operation wounds, burns, urological operations and umbilical infection (55 81 143, 172) but it can also occur without a clearly evident primary focus (55) Septicaemia due to *Pseudomonas*, like bacteraemia from other gram-negative bacilli, may be accompanied by endotoxin shock (172)

In the published series of *Pseudomonas* infections the reco ery and mortality incidences have varied over a wide range They have doubtlessly been influenced by marked differences n the susceptibility to infection of the various patient groups as well as by fairly great differences in treatment However mortality is almost without exception high in th e more se re forms of disease, such as peritonitis, meningitis and septicaemia, with incidences ranging from 20 to nearly

100 / (50, 55 77 155, 172) Endotoxin shock possibly associated with septicaemia greatly influences the prognosis. Mortality in *Pseudomonas* septicaemia among adults has been reported at bout 80 / when endotoxin shock was present, and at 20 / in ther cases (172)

Histologically the typical change in *Pseudomonas* infections is a diffuse acute vasculitis, with abundant bacteria on the vascular walls, and haemorrhages, thromboses and necroses in the adjacent tissues (55)

Epidemics Caused by *Pseudomonas*

In the non-hospital population the *Pseudomonas* is rarely the causati agent in primary infectious processes (55, 77 87 102, 129 177), nd epidemics are also of rare occurrence except in hospitals. However there are reports of diarrhoea epidemics due to infected milk or well water (47 145)

I hospitals, on the other hand, *Pseudomonas* ha been the cause f epidemics, some of which h been quite large, and these hospital infec tion ha increased considerably within the last tw decades (19, 50 56, 55 65). They have been quite numerous in newborn and praemature nurseries (10 21 22, 39 47 69, 72, 89 92, 94 113 116, 128, 132, 165, 167 178) and in urological and burns units (50, 81 99 106 108, 109 114 150 167) They have also been reported from other units (17 18 43 127 158, 159, 167 176)

For the onset f hospital infection with *Pseudomonas* there are certain preconditions, hich were brought out by Wahba in his investigation in 1965 (167) Using combined pyocine and serological typing method he studied the *Pseudomonas* strains in different kinds of hospital w rds. Where the *incidence of infection* was low the isol ted strains were often of v rious types presumably brought in by patients and the i fections were to great extent utogenic This situation he found in the eye, ear and surgical wards, whereas in the urological, burns nd paediatric units a certain strain often wa dominant for some length of time and an epidemic of clearly this type prevailed in the ward.

An essential factor in the onset of an epidemic appeared to be the number of infection-susceptible patients in the ward. When they were few in number the *Pseudomonas* spread slowly and the arious cases were caused by different types f *the micro-o ganism*. When there were many patients of this kind, some given strain became predominant and was the cause of numerous cases of infection in the course of weeks or months.

Wahba summarized the situation by stating that whenever highly susceptible patients came in contact with heavy disseminators of the organism, cross-infection was common (167)

Routes of Transmission of *Pseudomonas* Infection

It is apparent that the *Pseudomonas* bacterium can spread in arious w ys, as by contact, by air or by way of contaminated hosp tal equipment (56, 60, 175) The relative importance and share of these routes in the spread of the infection probably differ according to the hospital cond tions and the type of p tients.

Transmission by hands. A patient with burns, diarrhoea or urinary tract infection who is infected with *Pseudomonas* readily contaminates the hands f the nursing staff (54 99, 106) Often the bedding and urine bottles f these patients are also highly contaminated (54 99 106, 150) and handling them may probably also contaminate the hands.

Gram-negati e bacilli do not belong to the normal permanent bacterial flora of the *skin* and they disappear spontaneously (136, 177) However even this brief period may be sufficient for the organism to become transferred to another patient or to equipment. It has also been demonstrated that after massive contamination it is difficult to fully free the hands from the organism by washing and disinfectants, though its amount will be greatly decreased (100). Since *Pseudomonas* is able to survive and even to grow

Cases of urinary tract infection with *Pseudomonas* have been described in patients with indwelling catheter and in operated patients (55 106 108 150) Animal experiments have shown that obstruction or foreign bodies in the urinary tract predispose to infection even in the presence of a fully normal antibody level of the body (141)

The susceptibility to bacillary infections often seen in patients with leucaemia and aplastic anaemia and persons receiving radiotherapy or x ray treatment (15 19 25 56 75 166 167 176) is held to be largely a result of lowering of the general resistance of cells and depression of antibody formation by irradiation as well as by antimetabolites and cortisone (24 67 115 177)

Patients with chronic pulmonary processes and fibrosis of the pancreas have been observed to be sensitive to *Pseudomonas* infection (4? 72, 167 176) The basic disease in these cases probably lowers the resistance of the bronchial mucosa, rendering it easier for possible pathogenic pharyngeal bacteria to attack the bronchi (29 62, 86, 91)

It is a generally accepted opinion that antibiotic therapy predisposes to *Pseudomonas* infections (15 175 180) The basis may be that colonization is facilitated by disappearance of the sensitive normal mucosal flora and that, at least in the newborn, antibody formation is weaker owing to disappearance of the innocent intestinal flora of maternal origin (8 144 177) Experiments in vitro have also indicated that growth of some *Pseudomonas* strains is stimulated by tetracyclines or chloramphenicol (145)

Infections Due to *Pseudomonas*

The *Pseudomonas* may produce both localized infectious foci as well as systemic infection The incubation time is 5—7 days (116 155) When the infectious agent directly attacks the meninges (77) or the trachea (125 159) incubation requires only 1—2 days.

Infections of the ext rnal auditory canal and the middle ear are typical *Pseudomonas* infections (55 123, 165) However it is rarely encountered as the causative agent in acute otitis media being more common in chronic processes in the ear (30 55 87 122, 155) It can cause infections of the eye of various kinds, from conjunctivitis to panophthalmitis (18, 30, 55) Burns and operation wounds may become infected (15 30 55 99 177) and likewise the umbilical stump of the newborn infant (92, 143, 155) Associated with *Pseudomonas* infections there are a great variety of skin symptoms, being evidently secondary signs of the septicaemia and manifesting either as metastatic foci or toxic reactions (55)

The *Pseudomonas* has been found to give rise to respiratory tract infections of various kinds and degrees. Cases have been described of purulent rhinitis (115 155) bronchitis, pneumonia, abscess of the lungs and empyema (55 143, 155). It has been found to cause localized infectious foci on the pharyngeal mucosa and in the parotid glands (39 55) as well as infections of the lower alimentary tract, diarrhoea of varying degree, and peritonitis (30, 54 55 94 143, 155) It has also been responsible for urinary tract infections (30 55 177) and meningitis (30 55, 77)

All of the above conditions may lead to septicaemia, to which the newborn infant in particular is susceptible (55 56, 118, 143) Septicaemia has been found to develop especially on the base of infected operation wounds, burns, urological operations and umbilical infection (55 81 143 172) but it can also occur without a clearly evident primary focus (55) Septicaemia due to *Pseudomonas* like bacteraemia from other gram negative bacilli, may be accompanied by endotoxin shock (172)

In the published series f *Pseudomonas* infections the recovery and mortality incidences have varied over a wid range Tl ey ha e doubtlessly been influenced by marked d fferences in the susceptibility to infection of the various patient groups as well as by fairly great differences in treatment. However mortal ty is almost without exception high in the more se re forms of disease, such as peritonit s, meningitis and septicaemia with incidences ranging from 20 to nearly

myxin and bacitracin (30, 123) Sensitivity to chloramphenicol, tetracycline and streptomycin varies, but a rapid development of resistant strains has been observed (15, 30). This is probably due to the ability of gram-negative bacilli to acquire resistance against a drug, or even a number of drugs simultaneously by transferring resistance-carrying genetic factor from one strain to another (26, 170).

Good results have often been achieved in *Pseudomonas infections* with polymyxin and with colistin, an antibiotic drug of the same type (30, 56 77 125, 155) However a drawback in the use of polymyxin is its rather high toxicity while part of the *Pseudomonas* strains have been found to develop resistance towards the less toxic colistin (27 30, 131) The combination of chloramphenicol or tetracycline with polymyxin or colistin may nevertheless intensify their effect (74)

Two fairly new antibiotics, gentamicin (20 27 73, 157) and the semisynthetic penicillin derivative carbenicillin (28), have also proved effective in *Pseudomonas* infections. A synergetic effect can possibly be obtained by combined therapy using these two drugs, or one of them with other antibiotics (28) In vitro tests, however have already shown that some *Pseudomonas* strains develop resistance to gentamicin (20).

For topical treatment, not only antibiotics but also a number of *other antibacterial agents*, including chlorhexidine (51, 125) silver nitrate (52, 101) dilute acetic acid (126), and furazolium chloride (58), have been used with fairly good results.

In the case of patients with immunoglobulin deficiency ordinary and hyperimmune plasma (51 76, 81) and gamma-globulin (81 88, 157) have been used in the treatment and prophylaxis of *Pseudomonas* infection. In the future it may be possible to protect susceptible patient groups by vaccination (4 6)

It is obvious that an essential requirement for the prevention of hospital epidemics of *Pseudomonas* infection is meticulous hospital hygiene that takes into consideration the special nature of this genus of bacilli (50 89, 175). It appears to be of utmost importance to keep the hospital equipment and supplies free of the infective agent. A definitely reliable result can apparently be attained only through sterilization by autoclaving or with ethylene oxide (176). In the cleaning of equipment that cannot be sterilized in this manner fairly good results have been obtained with, among other substances, sodium hypochlorite (21 175), iodophores (89), dilute acetic acid (9 45) glutaraldehyde (65 71 156) and chlorhexidine (175).

in the hospital environment at room temperature if some humidity and organic material is available (16 70 105 111 117) a small amount of bacteria may through the medium of fomites lead to an ultimately massive infection.

Transmission by equipment and supplies By various methods of typing, epidemic strains of *Pseudomonas* have been demonstrated in hospital equipment and medical supplies, and the epidemic has subsided when the source of infection has been destroyed (17 18 22, 159) Although in very many of the earlier studies it was not possible, in the absence of a typing method, to demonstrate that the *Pseudomonas* isolated from the equipment was of the epidemic type the ceasing of the epidemic after disappearance of the source of infection indicates that this probably was the case in also these instances (69 114 165 178) It is presumable that contaminated hospital equipment and nursing supplies have been the most significant factor in the development of most epidemics.

Among hospital equipment particularly susceptible to *Pseudomonas* colonization are all items that stay moist or are difficult to clean. The organism has been isolated from oxygen equipment (45 89 104) suction apparatuses (22 89 96 139) nebulization equipment (45 89 92 110 111 112 134) incubators (21 89 92, 96 146) resuscitation equipment and respirators (89 125) various parts of anaesthesia equipment (65 153 179) and heart lung machines (85)

Spread of the infection has been observed to have occurred by means of various contaminated medicines (19 117 121 128) bandaging material (158) and water that was believed to be sterile (89 159 178)

It has also been observed that various disinfectants may be infected with *Pseudomonas* sometimes quite heavily Quaternary ammonium compounds are in themselves poorly effective against this organism (175 177) and their action is lowered by numerous substances such as proteins, cellulose and cork (98 120 127) to such an extent that the solution or the materi ls stored in it may become contaminated (127) The tannin in bark corks has been observed to lower the effect of also chlorhexidine (95, 109) so that instead of the expected disinfection there may have occurred transmission of infection by the solution.

Hexachlorophene which is in wide use for the disinfection of the hands, also possesses a relatively weak action against *Pseudomonas* (85, 100) and the organism has been encountered in soaps (11) hand creams (85) and shampoos (17) containing hexachlorophene and in hexachlorophene dispensers (89)

Kitchen sinks, cupboards and dishes have been found to be contaminated with *Pseudomonas* (99 148) and may have been responsible for spreading of the infection.

Transmission by air and dust. Although *Pseudomonas* is not properly a dust bacterium, it appears to be able to survive in the hospital environment for long periods after once entering it (70 99) It has not been encountered ordinarily in hospital air (45 107 168) but during epidemics it has been present even in large numbers, in samples of the air (99 116 130 176) Air humidifiers may also promote transmission of the organism by air (11 45)

Carriers of P s e u d o m o n a s. Carriers of *Pseudomonas* in the hospital staff probably play but a small part in the onset and spread of hospital epidemics, since such carriers have been quite few in number even during epidemics (18, 22 99) On the other hand faecal carriers among the patients have been found to be probable disseminators of *Pseudomonas* (148) This possibly is ascribable to contamination of hands or equipment in connection with care and treatment, and is less likely to occur when the bacteria carriers are healthy members of hospital personnel.

Treatment and Prophylaxis of *Pseudomonas* Infection

Pseudomonas organisms have generally been found to be highly resistant to the commonly used antibiotics, as penicillin, ampicillin, eryth

mycin and bacitracin (30, 125). Sensitivity to chloramphenicol, tetracycline and streptomycin arises, but a rapid development of resistant strains has been observed (15, 30). This is probably due to the ability of gram-negative bacilli to acquire resistance against drug, or even a number of drugs simultaneously by transferring a resistance-carrying genetic factor from one strain to another (26, 170).

Good results have often been achieved in *Pseudomonas* infections with polymyxin and with colistin, an antibiotic drug of the same type (30, 55, 77 123, 135). However a drawback in the use of polymyxin is its rather high toxicity while part of the *Pseudomonas* strains have been found to develop resistance towards the less toxic colistin (27 30, 131). The combination of chloramphenicol or tetracycline with polymyxin or colistin may nevertheless intensify their effect (74)

Two fairly new antibiotics, gentamicin (20, 27 73 157) and the semisynthetic penicillin derivative carbenicillin (28) have also proved effective in *Pseudomonas* infections. A synergetic effect can possibly be obtained by combined therapy using these two drugs, or one of them with other antibiotics (28) In vitro tests, however have already shown that some *Pseudomonas* strains develop resistance to gentamicin (20)

For topical treatment, not only antibiotics but also number of other antibacterial agents, including chlorhexidine (31 123), silver nitrate (32, 101) dilute acetic acid (126) and furazolium chloride (58) have been used with fairly good results.

In the case of patients with immunoglobulin deficiency ordinary and hyperimmune plasma (51 76, 81) and gamma globulin (81 88, 137) have been used in the treatment and prophylaxis of *Pseudomonas* infection. In the future it may be possible to protect susceptible patient groups by vaccination (4 6).

It is obvious that an essential requirement for the prevention of hospital epidemics of *Pseudomonas* infection is meticulous hospital hygiene that takes into consideration the special nature of this genus of bacilli (30, 89, 175). It appears to be of utmost importance to keep the hospital equipment and supplies free of the infective agent. A definitely reliable result can apparently be attained only through sterilization by autoclaving or with ethylene oxide (175) In the cleaning of equipment that cannot be sterilized in this manner, fairly good results have been obtained with, among other substances, sodium hypochlorite (21 175) iodophores (89), dilute acetic acid (9 45) glutaraldehyde (65, 71 158) and chlorhexidine (175)

in the hospital environment at room temperature if some humidity and organic material is available (16 70 103 111 117) a small amount of bacteria may through the medium of fomites lead to an ultimately massive infection.

Transmission by equipment and supplies. By various methods of typing, epidemic strains of *Pseudomonas* have been demonstrated in hospital equipment and medical supplies, and the epidemic has subsided when the source of infection has been destroyed (17 18 22, 159) Although in very many of the earlier studies it was not possible, in the absence of a typing method, to demonstrate that the *Pseudomonas* isolated from the equipment was of the epidemic type, the ceasing of the epidemic after disappearance of the source of infection indicates that this probably was the case in also these instances (69 114 165 178) It is presumable that contaminated hospital equipment and nursing supplies have been the most significant factor in the development of most epidemics.

Among hospital equipment particularly susceptible to *Pseudomonas* colonization are all items that stay moist or are difficult to clean. The organism has been isolated from oxygen equipment (43 89 104) suction apparatuses (22, 89 96 139) nebulization equipment (45 89 92, 110 111 112 134) incubators (21 89 92, 96, 146) resuscitation equipment and respirators (89 125) various parts of anaesthesia equipment (65 153 179) and heart lung machines (83)

Spread of the infection has been observed to have occurred by means of various contaminated medicines (49 117 121 128) bandaging material (158) and water that was believed to be sterile (89 159 178)

It has also been observed that arious disinfectants may be infected with *Pseudomonas* sometimes quite heavily Quaternary ammonium compounds are in themselves poorly effective against this organism (175 177) and their action is lowered by numerous substances such as proteins, cellulose and cork (98 120 127) to such an extent that the solution or the materials stored in it may become contaminated (127) The tannin in bark corks has been observed to lower the effect of also chlorhexidine (95, 109) so that instead of the expected disinfection there may have occurred transmission of infection by the solution.

Hexachlorophene which is in wide use for the disinfection of the hands, also possesses a relatively weak action against *Pseudomonas* (85, 100) and the organism has been encountered in soaps (11) hand creams (85) and shampoos (17) containing hexachlorophene and in hexachlorophene dispensers (89)

Kitchen sinks, cupboards and dishes have been found to be contaminated with *Pseudomonas* (99 148) and may have been responsible for spreading of the infection.

Transmission by air and dust Although *Pseudomonas* is not properly a dust bacterium, it appears to be able to survive in the hospital environment for long periods after once entering it (70 99) It has not been encountered ordinarily in hospital air (45 107 168) but during epidemics it has been present, even in large numbers, in samples of the air (99 116, 130 176) Air humidifiers may also promote transmission of the organism by air (11 45)

Carriers of P s e u d o m o n a s. Carriers of *Pseudomonas* in the hospital staff probably play but a small part in the onset and spread of hospital epidemics, since such carriers have been quite few in number even during epidemics (18, 22, 99) On the other hand faecal carriers among the patients have been found to be probable disseminators of *Pseudomonas* (148) This possibly is ascribable to contamination of hands or equipment in connection with care and treatment, and is less likely to occur when the bacteria carriers are healthy members of hospital personnel

Treatment and Prophylaxis of *Pseudomonas* Infection

Pseudomonas rganism have generally been found to be highly resistant to the commonly used antib otics, as penicillin, ampicillin, ryth

romysin and bacitracin (30, 125). Sensitivity to chloramphenicol, tetracycline and streptomycin ... ares, but a rapid development of resistant strains has been observed (15, 30). This is probably due to the ability of gram-negative bacilli to acquire resistance against drug, or even a number of drugs simultaneously by transferring a resistance-carrying genetic factor from one train to another (26, 170).

Good results ha e often been achieved in *Pseudomonas* infections with polymyxin and with colistin, an antibiotic drug of the same type (30, 55, 77 123, 153). However, a drawback in the use of polymyxin is its rather high toxicity while part of the *Pseudomonas* strains ha e been found to develop resistance towards the less toxic colistin (27 30 131). The combin tion of chlor amphenicol or tetracycline with polymyxin or colistin may nevertheless intensify their effect (74)

Tw fairly new antibiotics, gentamicin (20, 27 73, 157) and the semisynthetic penicillin deriva tiv carbenicillin (28), ha also proved effective in *Pseudomonas* infections. A synergetic effect an possibly be obtained by combined therapy using these tw drugs, or one of them with other antibiotics (28) In itro tests, however ha already shown that some *Pseudomonas* strains develop resistance to gentamicin (20)

For topical treatment, not only antibiotics but also number of other antibacterial agents, including chlorhexidine (51 125) sil er nitrate (32, 101), dilute acetic acid (126) and furazolium chloride (58) ha e been used with fairly good results.

In the case of patients with immunoglobulin deficiency ordinary and hyperimmune plasma (51 76, 81) and gamma globulin (81 88, 157) hav been used in the treatment and prophylaxis of *Pseudomonas* infection. In the future it may be possible to protect susceptible patient groups by vaccination (4 6).

It is obvious that an essential requirement for the prevention of hospital epidemics of *Pseudomonas* infection is meticulous hospital hygiene that takes into consideration the special nature of this genus f bacilli (50, 89 175). It ppears to be f utmost importance to keep the hospital equipment and supplies free of the infectiv agent. A definitely reliable result can apparently be attained only through sterilization by autoclaving or with ethylene oxide (175) In the cleaning f equipment th t cannot be *sterilized in this manner fairly good results* ha e been obtained with, among other substances, sodium hypochlorite (21 175) iodophores (89) dilute acetic acid (9 45), glutaraldehyde (65, 71 158) and chlorhexidine (175)

Object of Investigation

The investigation presented here was undertaken with the object

1) to study the occurrence of the *Pseudomonas* bacillus in a paediatric surgical unit treating children under 2 years of age

2) to study the relationship between *Pseudomonas* colonization and *Pseudomonas* infections, and their significance for the surgical paediatric patient and

3) to clarify the routes and modes of transmission of *Pseudomonas* infection.

Material and Methods

Material

The present investigation was carried out during the 12-month period from October 1, 1962 to September 30, 1963 in the surgical unit of the Children's Hospital of the Helsinki University Central Hospital. This unit has 22 beds for children under 2 years of age. During 1962 the impression had been gained clinically supported by numerous findings of *Pseudomonas* infection in autopsied patients (132) that there was a *Pseudomonas* epidemic of hospital infection type in the unit. Opinions varied concerning the importance that should be attached to the epidemic, the prevailing opinion being that the *Pseudomonas* was a saprophyte of no noteworthy consequence for the patient.

For this reason, *Pseudomonas*-colonized children were not isolated either in the ward or in the operation room. This was the situation during the first three months of the present study, from October 1 to December 31, 1962. After the latter date efforts were made to prevent spread of the infection by isolating the patients in whom *Pseudomonas* bacilli were found and by intensifying of the cleansing and sterilization of the equipment used in the care and treatment of these patients.

During the period of this investigation a total of 513 surgical patients were hospitalized in the unit. They varied in age from a few hours to about 2 years. Samples were taken on admission from each patient's nose and throat for bacterial culture. This was repeated one or more times in the case of children suspected of being particularly susceptible to infection, such as patients in poor condition and newborn infants. Urine samples from urological patients were examined twice a week. Upon onset of any signs of infection in the patient samples pertinent to the symptoms were immediately taken. A total of 2,771 bacterial culture samples were examined.

Nose and throat swabs were taken six times from the surgical staff and four times from the ward personnel. These samples totalled 511.

Samples for bacterial culture were taken at intervals of 1–2 months from [illegible] part of the equipment and environment in the operating room and the ward. Other equipment was sampled according to use and when there was particular reason to suspect contamination. The air was examined eight times in the operating room and twice in the ward. A total of 1072 samples were examined.

Methods

Sample taking and culture. Samples from the nose and throat and of pus were taken with a dry sterile cotton swab. All the urine samples were drawn by catheter. A sample of bronchial mucus was taken from the sterile glass connecting tube when the bronchial toilette was being done. In autopsied cases a sample was taken from the lungs for bacterial culture, as described by Rantasalo and Hjelt (132).

The samples from the hospital equipment and environment were taken mostly with sterile dry cotton swabs. Swabs dipped in sterile saline solution were used for a part of the dust samples from furniture and floors. In the case of suction bottles, oxygen equipment, incubators, nebulizers, respirators and anaesthesia equipment a number of samples were taken from different parts of the fomite, particularly from areas that are difficult

Object of Investigation

The investigation presented here was undertaken with the object

1) to study the occurrence of the *Pseudomonas* bacillus in a paediatric surgical unit treating children under 2 years of age

2) to study the relationship between *Pseudomonas* colonization and *Pseudomonas* infections, and their significance for the surgical paediatric patient, and

3) to clarify the routes and modes of transmission of *Pseudomonas* infection

Material and Methods

Material

The present investigation was carried out during the 12-month period from October 1 1962 to September 30, 1963 in the surgical unit of the Children Hospital of the Helsinki University Central Hospital. This unit has 22 beds for children under 2 years f age. During 1962 the impression had been gained clinically supported by numerous findings of *Pseudomonas* infection in utopsied patients (132), that there was *Pseudomonas* epidemic of hospital infection type in the unit. Opinions aried concerning the importanc that should be attached to the epidemic, the prevailing opinion being that the *Pseudomonas* was saprophyte of no noteworth consequence for the patient.

For this reason, *Pseudomonas*-colonized children were not isolated either in the ward or in the operation room. This was the situation during the first three months f the present study from October 1 to December 31 1962. After the latter date fforts were made to prevent spread of the fection by isolating the patients in whom *Pseudomonas* bacilli were found and by intensif ng of the cleansing and sterilization f the equipment used in the care and treatment of these patients.

During the period of this investigation total of 513 surgical patients were hospitalized in the un t They aried in age from few hours to about 2 y rs Samples were taken on admission f m each patient nose and throat for bacterial ulture This was epeated one or more times in the ase of hildren suspected f being partic l rl susceptible to infection, such as patients in poor condition and newborn infants. Urine samples from urological patients were examined twice week. Upon onset of any signs of infection in patient samples pertinent to the symptoms were immediately taken. A total of 2,771 bacterial culture samples were examined.

Nose and throat swabs were taken six times from the surgical staff and four times from the ward personnel. These samples totalled 511

Samples for bacterial culture were taken at intervals of 1–2 months from a part of the equipment and en ironment in the operating room and the ward. Other equipment was sampled according to use and when there was particular reason to suspect contamination. The air was examined eight times in the operating room and twice in the ward. A total of 107[illegible] samples were examined.

Methods

Sample taking and culture. Samples from th[e] nose and throat and of pus were taken with a dry sterile cotton swab. All the urine samples wer[e] drawn by catheter A sample of bronchial mucu[s] was taken from the sterile glass connecting tub[e] when the bronchial toilette was being done. I[n] utopsied cases a sample was taken from th[e] lungs for bacterial culture, as described by Ran[-]taselo and Hjelt (132).

The samples from the hospital equipment an[d] environment were taken mostly with sterile dr[y] cotton swabs. Swabs dipped in sterile salin[e] solution were used for a part f the dust sample[s] from furniture and floors. In the case of suctio[n] bottles, oxygen equipment, incubators, nebulizer[s] respirators and anaesthesia equipement a numbe[r] f samples were taken from different parts of th[e] fomite, particularly from areas that are difficul[t]

to clean or that stay moist. For collection of air borne bacteria, blood agar dishes 9.5 cm in diameter were placed in all the rooms and kept exposed for 2–12 hours, usually during the busy working hours.

Culture of the samples was carried out in the hospital's laboratory. Samples of urine were allowed to drip directly from the catheter onto blood agar dishes. The faeces samples were grown on SS agar (Difco) and Drikalsky agar and in selenite tubes. The bacterial cultures from all the other samples were made on blood agar in liver broth or in semisolid nutrient agar. The cultures were personally examined by the writer after 24 hours incubation, and negative cultures were incubated for a further 24 hours.

Identification. A tentative identification of the bacterial growth was made in the hospital's laboratory on the basis of staining, appearance of the colonies, haemolytic capacity, pigment formation and odour. Preparatory biochemical examinations were made of all gram negative rod bacteria in triple sugar iron-agar, urea agar and motility tubes. All the strains obtained were then sent to the State Serum Institute, Helsinki, where the final species determination was carried out.

As *Pseudomonas* bacilli were regarded all gram negative rod bacteria provided they used no sugars other than possibly glucose, were motile, formed a green pigment, liquefied gelatin, and did not produce indole. Other gram negative rod shaped organisms were identified according to the formula of Kauffmann (80).

All phosphatase-positive *Staphylococci* were also tested for the production of coagulase, and positive strains were regarded as *Staphylococcus aureus*.

Statistical analysis. In statistical comparisons of the results the Chi analysis was used as a four squares test (3). The difference was considered to be highly significant when $P<0.1$ %, significant when $P<1$ %, and almost significant when $P<5$ %.

Results

Occurrence of *Pseudomonas* during the Present Study

A Patients

Time distribution. *Pseudomonas* bacilli were isolated from 202 f the 2,771 samples taken from patients in the surgical unit f the Children Hospital. The 202 samples were from 53 patients, who comprised 10.5 / f the 515 patients under tre tment in the unit during the period f the present study.

Table 1 and Fig. 1 show the monthly distribution of the patients found to be colonized with *Pseudomonas*. The largest number of cases oc urred t the beginning and the end f the period studied. In October-November-December 1962 and August-September 1963, 37 (16 /) of the patients nder treatment were colonized, whe as there were only 16 colonized patients (6) d ring the intervening seven months. The diff rence between these umbers is statistically h ghl gnificant.

Deaths during the studied period and Pseu d mona colonization. Seventeen of the 55 *Pseudomonas*-colonized patients died. In 16 of these cases the organism was isolated in cultures f lung samples taken t autopsy. In one case the culture from the lung was negati e, but *Pseudomonas* had been identified in wound pus during lif The lung culture ga the only positive finding f *Pseudomonas* in 6 cases. With one exception the deaths of *Pseudomonas*-colonized infants were concentrated to the first months and last months f the period studied (Table 1 and Fig. 1). Eleven of 23 colonized children died during the first 5 months, and 6 died of the 30 colonized children who were hospitalized later. The difference is highly significant.

A total of 41 deaths occurred among the 515 patients treated in the surgical unit at the time f this in estigation. In 16 f these cases (39 / f deaths) the bacterial culture f the lung sample was positi for *Pseudomonas*, as said above. Of the total f 19 children who died during the

TABLE 1 *Number of P d m s-colonized patients and f deaths among them, as compared t non-colonized pat ents and all patients, by months.*

Year	1962			1963									
Month	Oct	Nov	Dec	Jan	Feb	Mar	Apr	M y	June	July	Aug	Sept.	Total
Pseudomonas colonized patients	9	7	7	2	1	5	4	0	5	1	5	9	55
Number of deaths	5	3	3	0	0	0	1	0	0	0	2	3	17
Non- olonized pa ents	47	36	8	49	36	27	37	38	6	43	33	40	460
N mber of death	3	2	3	3	2	1	1	3	1	4	0	1	24
T al umber f pa	[illegible]	43	[illegible]	51	37	32	41	[illegible]	39	44	38	49	515
Numb of deaths	8	5	6	3	2	1	2	3	1	4	2	4	41

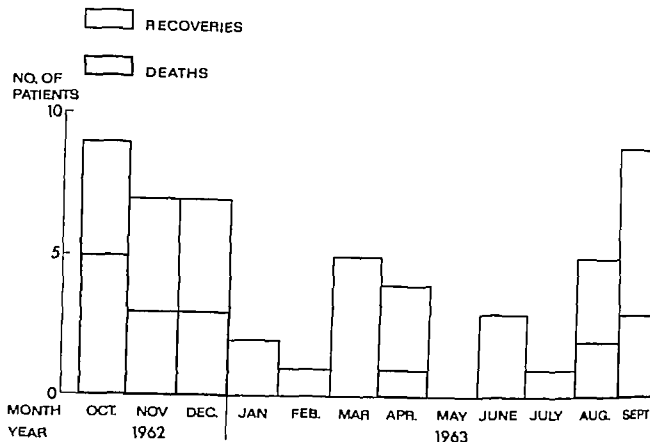


Fig 1 \umber of P s e u d o ı ı o n a s-colon zed patients, by months.

first 3 months of this investigation 10 had a *Pseudomonas* positive lung culture while this was the case in only 6 instances among the 22 children who died during the remainder of the study period

During the same 12 months, *I seudomonas* was isolated at autopsy from 5 of the 14 infants who died in the praematures ward and from 3 of the 20 children who lied in the infection ward for children under 2 years. These figures differ sig nificantly from the *Pseu lomon s* colonization figures in the paediatric surgical unit studied

P s e u d o n o n a s infections An infection caused by *Pseudomon s* bacilli was diagnosed in 32 childre whi h is equ al nt to 6 2 % of all the pati nts treated in th unit The n mber of cl ildren exhibitn g s gn of nfection was highest during the first 3 n onths of the study diff n ig almost s gnificantly f om th number of cases d agnosed later (Tabl 2 and Fig 2) On the oth r hand the incidence of *I seudomon s* carriers without symptoms was approximately the sam in the two periods tated i.e., 12 % and 11 % respectiv ly

Time of fi iding of coloni ation The isolation of *I seudomonas* bacilli in a patient during the first two days of hospitalization in the surgical unit wa r garded as a sign that there had been colonization lready on ad mis ion. Such cases numbered) or 1 9 % of all children treated in th unit, l they were approximately evenly d tributed th period tudied (Table 3 and Fig 3)

All the ch l lren who were col ı iz d on admission t th u t eld r l ad been tran ferred directly from t l hosp it l u nt were re hosp italized after ha g bee ı t h e for 2 month at th most

\ f nd ng of ol m t ı w th *I seı dom nas* was n de lat tl ı tl secon d l y m 28 ch ldren ı 5 5 f all l ild en m ler t eat ı nt. Samp les h d n t bee taken arli r fı m ı of these hildre 3 of whom w re ı l ı at ent d ring the f rst 3 nth f th t id ed

TABLE 2. Number of *Pseudomonas* infections among the colonized patients, by months.

Year	1962			1963									
Month	Oct.	Nov	Dec.	Jan.	Feb.	Mar	Apr.	May	June	July	Aug.	Sept.	Total
Pseudomonas-colonized patients													
Without symptoms	0	2	4	1	0	3	2	0	2	1	2	4	21
With symptoms of infection	9	5	3	1	1	2	2	0	1	0	3	5	32
Non-colonized patients	47	36	38	49	56	27	37	58	56	43	53	40	460
Total number of patients	56	43	45	51	57	32	41	58	59	44	58	49	513

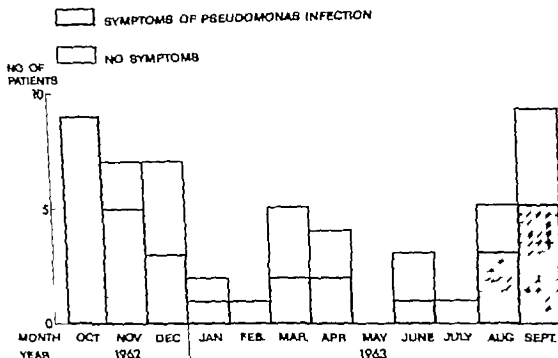


Fig. ... Oc urren of P... infections among the colonized patients, by months

... riod. The ... umber ... f children ... olonized in the ... was highest during the first 3 months, ... children or ... of ... ll children ... ted in the un... t during that time. During the ... mainder ... f the studied period there were only ... lonized ... hildren or 3.3 ... The difference ... statistically highly significant. Of the latter 12 children ... were hospitalized in the unit during the first part of the stated period and 6 during the last 2 months (Table 3 and Fig. 3).

B. Hospital Personnel

Pseudomonas did not grow from the 251 nasal and 260 throat samples taken from the ward personnel and the surgical staff.

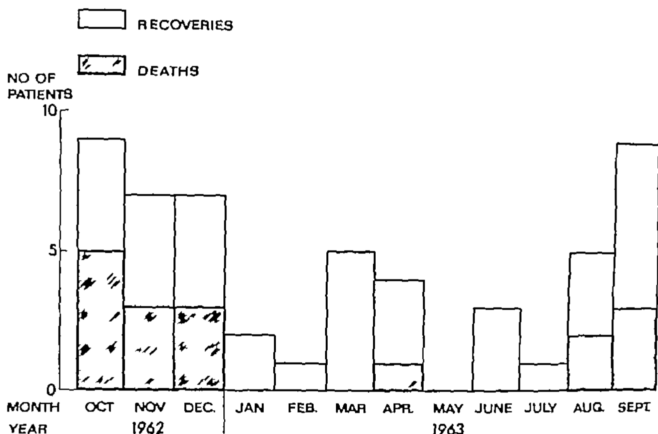


Fig 1 Number of Ps udomona -coloni ed patients, by months.

first 3 months of this investigation 10 had a *Pseudomonas* positive lung culture while this was the case in only 6 instances among the 22 children who died during the remainder of the study period.

During the same 12 months, *Pseudomonas* was isolated at autopsy from 5 of the 14 infants who died in the praematures ward and from 3 of the 20 children who died in the infection ward for children under 2 years. These figures differ sig nificantly from the *Pseudomonas* colonization figures in the paediatric surgical unit studied.

Pseudomonas infections An infection caused by *Pseudomonas* bacilli was diagnosed in 32 children, which is equivalent to 6 2 % of all the pati nts treated in the unit The number of children exh biting s gn of infection was highest during the first 3 months of the study differing almost significantly from the number of cases diagn sed later (Table 2 and Fig. 2) On the other hand the incidence of *Pseudomonas* carri rs without symptoms was approximately the same in the two periods stated, i 12 % and 4 1 %, respectively

Time of fin ling of coloni ation The isolation of *Pseudomonas* bacilli in a patient during the first two days of hospitalization in the surgical unit was r garded as a sign that there had been colonization already on admission. Such cases numbered 2 or 1.9 % of all children treated in the unit, and they were approximately evenly distributed over the period studied (Table 3 and Fig 3)

All the children who were colonized on admis sion to the unit either had been transferred directly from other hospital units or were re-hospital zed after having been at home for 2 months at the most.

A finding of colonization with *Pseudomonas* was ma le lat r tl an on the second day in 28 ch ldren i.e 5 5 % of all children under treat ment. Samples had n t been taken earlier from 5 of th se hildren 3 of whom were under treat men t luring the first months of the stud d

TABLE 2. Number of Pseudomonas infections among the colonized patients by months.

Year	1962			1963									
Month	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Total
Pseudomonas-colonized patients													
Without symptoms	0	2	4	1	0	3	2	0	2	1	2	4	21
With symptoms of infection	9	5	3	1	1	2	2	0	1	0	3	5	32
Non colonized patients	47	36	38	49	36	27	37	38	36	43	33	40	460
Total number of patients	56	43	45	51	37	32	41	38	39	44	38	49	513

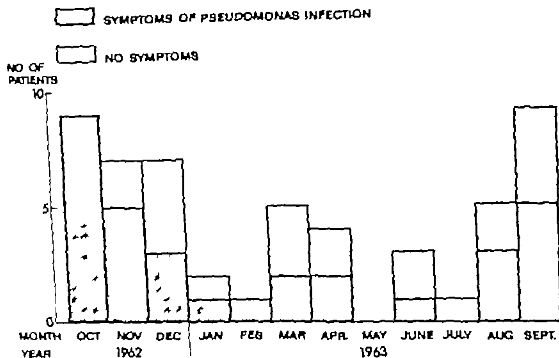


Fig. 2. Occurrence of Pseudomonas infections among the colonized patients, by months.

period. The number of children colonized in the unit was highest during the first 5 months, totalling 16 children, or 11 % of all children treated in the unit during that time. During the remainder of the studied period there were only 12 colonized children, or 5.5 %. The difference is statistically highly significant. Of the latter 12 children, 6 were hospitalized in the unit during the first part of the stated period and 6 during the last 2 months (Table 5 and Fig. 5).

B. Hospital Personnel

Pseudomonas did not grow from the 251 nasal and 200 throat samples taken from the ward personnel and the medical staff.

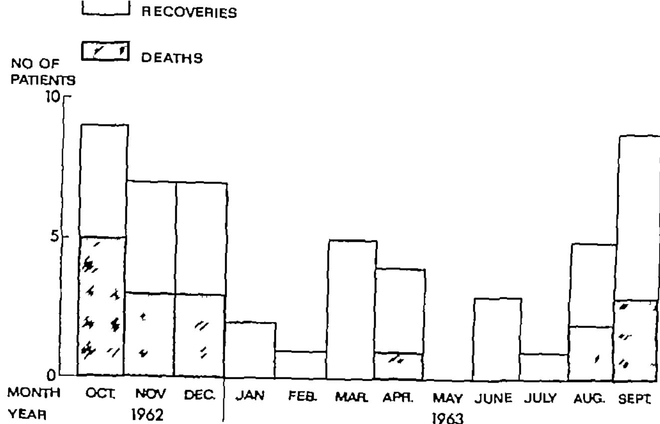


Fig. 1. Num ber of P s e u d o m o n a s-coloni ed patients, by months.

first ɔ months of this investigation, 10 had a *Pseu lomonas* positive lung culture while this was the case in only 6 instances among the 22 children who died during the remainder of the study period

During the same 12 months, *Pseudomonas* was isolated at autopsy from 5 of the 44 infants who died in the praematures ward and from 5 of the 90 children who died in the infection ward for children under 2 years. These figures differ sig nificantly from the *Pseudomonas* colonization figures in the paediatric surgical unit studied

P s e u d o m o n a s infections An infection caused by *Pseudomonas* ba illi was diagnosed in 52 children which i equivalent to 6 2 % of all the patients treated in the unit The number of children exhibiting sig s of infection was highest during the first 3 months of the study differing almost sign ficantly from the number of cases diagnosed later (Table 2 and Fig 2) On the other hand the incidence of *Pseu lomonas* carriers without symptoms was approximately the same in the two periods stated, i.e. 1.2 % and 4 1 % respectively

Time of finding of colon ation. The isolation of *Pseudomonas* bacilli in a patient during the first two days of hospitalization in the surgical unit wa r garded as a sign that there had been colonization already on admission. Such cases numbered 2 or 1 9 % of all children treated in the unit, an l th y wer approximately evenly distributed o er th period studied (Table 3 and Fig 3)

All the cl l lren wl o wer colonized on admis- ion to the u it tl h d been transferred directly from ther hosp t l unit or were re hospital zed aft r having been at home for 2 mo ths at th most

A finding of colon tion w tl *I seu lomonas* w is made lat r than on the seco l day in 28 childre i , 5 % of all hil lren und r tr at men L Samples l a l not been taken earli r f om 5 of these cl ildren 3 of wl o i v re t l r tre t n nt d ri g the first 3 mo tl of th studied

TABLE 2. Number of *Pseudomonas* infections among the colonised patients, by months

Year	1962			1963									
Month	Oct.	Nov	Dec.	Jan.	Feb.	Mar	Apr	May	June	July	Aug	Sept.	Total
Pseudomonas-colonised patients													
Without symptoms	0	2	4	1	0	5	2	0	2	1	2	4	21
With symptoms of infection	9	5	3	1	1	2	2	0	1	0	3	5	32
Non-colonised patients	47	36	38	49	56	27	57	58	36	45	5	60	460
Total number of patients	56	43	45	1	57	32	61	58	39	44	38	49	513

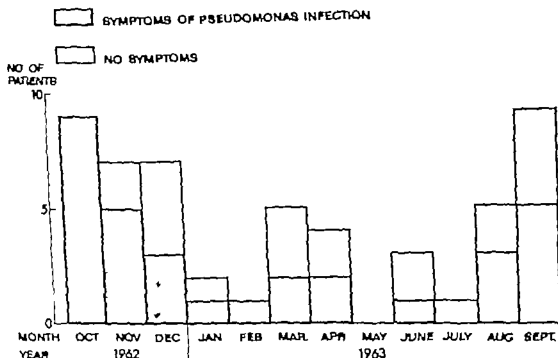


Fig. 2 Occurrence of *Pseudomonas* infections among the colonised patients, by months.

period. The number of children colonised in the unit was highest during the first 3 months, totalling 16 children, or 11 % of all children treated in the unit during that time. During the remainder of the studied period there were only 12 colonised children, or 3.3 %. The difference is statistically highly significant. Of the latter 12 children, 6 were hospitalized in the unit during the first part of the stated period and 6 during the last 2 months (*Table 3 and Fig. 3*).

B. Hospital Personnel

Pseudomonas did not grow from the 251 nasal and 260 throat samples taken from the ward personnel and the surgical staff.

TABLE 5 *Pseudomonas-colonized patients classified according to time of diagnosis of colonization by months*

Year	1962			1963									
Month	Oct.	Nov	Dec.	Jan.	Feb	Mar	Apr	May	Jun	July	A g	Sept.	
Pseudomonas-colonized patients													
Colonized on admission	5	2	2	1	0	3	2	0	[illegible]	1	3	5	
Colonized lat r	6	5	6	1	1	2	2	0	0	0	2	1	
Non-colonized patients	47	36	38	49	30	27	37	38	36	13	33	40	1
Total number of patients	56	43	45	61	37	32	41	58	39	14	38	19	5

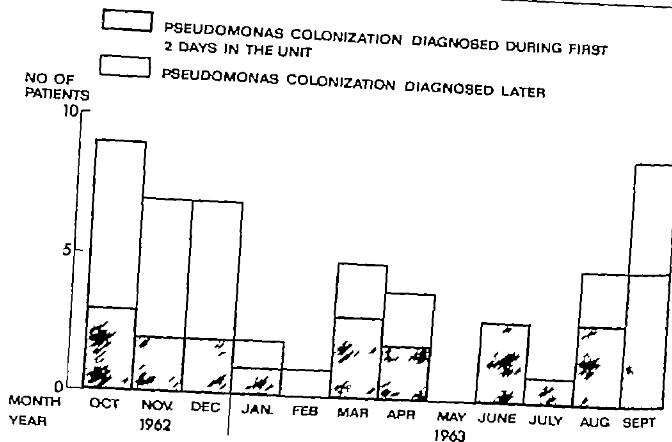


Fig 3 P eudo onas-coloniz d patients classif ed according t t f d agnos f olon zation b months

C Samples from the Environment Equipment and Air

The environments and founites in the ward unit and the operating unit examined for *Pseudomonas* and the time of each sample-taking ar stated in Table 1 Heavy contamination of the equipment and env onm nt wa revealed during th first 3 months of th invest gation period At this time *Pseudomonas* was found in many items i the operati g and th ward units In the first mentioned the orga bi i grew from samples taken fr m th e rubb

of an an esthesia ma

TABLE 1 Bacterial studies of hospital equipment, environment and air, carried out in the paediatric hospital during the period of study, by month

Object examined	1962 Oct	Nov	Dec	196 Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Total number of samples	Number Pseudomonas-positive
Operating unit														
Anaesthesia machines		+	−	−			−		−			−	99	2
Other equipment, furniture	−	−	−	−			−		−			−	72	0
Paste plates, polythene catheters	−	−	−	−	−	−	−	−	−	−	−	−	150	0
Stationary washbasins		+		−			−		−			−	38	1
Brushes		−	−	−			−		−			−	20	0
Ward														
Incubators	−	−	+	−	−	−	−	−	−	−	−	−	67	1
Nebulizers		−		−			−				−	−	12	0
Oxygen humidifiers		−					−				−	−	14	0
Suction apparatus	−						−				−	−	15	0
Suction catheters	−	−		−			−				−	−	22	0
Respirator			−								−	−	11	0
Glass bottles for drip-feeding				+	−						−		8	1
Feeding tubes	−			−	−						−		10	0
Fan jars	−	−					−				−	−	31	0
Hand cream jars			−										4	0
Stationary washbasins														
Patient rooms		+	−	−		+	−	−	−	−	+	+	74	9
Sluice room		−	−	−		−	−	−	−	−	−	+	15	1
Kitchen		+	−	−		−	−	−	−	−	−	+	17	2
Other rooms		−	−	−		−	−	−	−	−	−	−	23	0
Bathtubs		−	−	−		+	−	−	−	−	−	+	44	2
Brushes														
Kitchen		+	−	−		−	−	−	−	−	−	−	29	1
Examination room		−	−	−		−	−	−	−	−	−	−	21	0
Sluice room		+	−	−		−	−	−	−	−	−	−	34	2
Floor brushes		−	−	−		−	−	−	−	−	−	−	17	0
Room pails		−	−	−		−			−			−	11	0
Floor dust		−		−		−					−		15	0
Air (settling plates)														
Ward		−					−						18	0
Operating unit	−	−		−			−		−	−	−	−	178	0
Number of samples examined	48	185	81	83	56	19	83	27	111	158	87	96	1072	
Number *Pseudomonas*-positive	0	11	1	1	0	5	0	0	0	0	1	5		22

− = No growth of *Pseudomonas* in cultures.
+ = Growth of *Pseudomonas* in cultures. Exponent indicates the number of samples positive for *Pseudomonas*.

TABLE 3 *Pseudomonas-colonized patients classified according to time of diagnosis of colonization by months*

Year	1962			1963									
Month	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Total
Pseudomonas colonized patients													
Colonized on admission	3	2	2	1	0	3	2	0	3	1	3	5	[illegible]
Colonized later	6	5	5	1	1	2	2	0	0	0	2	[illegible]	28
Non-colonized patients	47	36	38	49	56	27	37	38	56	43	33	40	[illegible]
Total number of patients	56	43	45	51	57	32	41	38	59	44	38	49	[illegible]

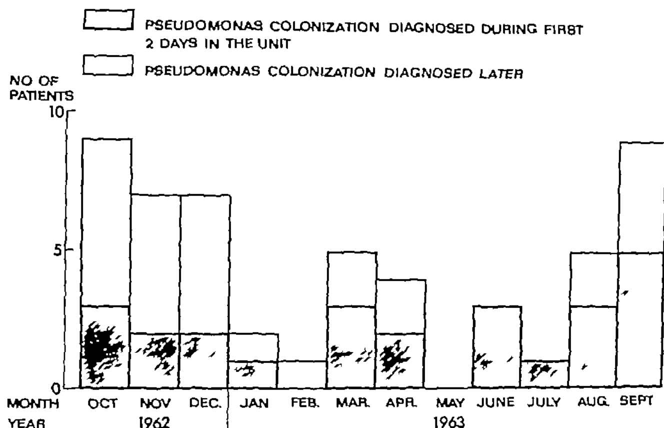


Fig. 3. Pseudomonas-colonized patients classified according to time of diagnosis of colonization, by months.

C. Samples from the Environment, Equipment and Air

The environments and fomites in the ward unit and the operating unit examined for *Pseudomonas* and the time of each sample-taking are stated in Table 4. Heavy contamination of the equipment and environment was revealed during the first 3 months of the investigation period. At this time *Pseudomonas* was found in many items in the operating and the ward unit. In the first mentioned the organism grew from samples taken from the rubber tube and tube connector of an anaesthesia machine and from the mouth

and 3 during the last 2 months of this study Among the 8 non-colonized newborn there were 16 deaths, which were fairly evenly distributed over the study period.

Time of colonization. Pseudomonas bacilli ere found in 6 neonates d ring the first 2 days in the surgic l unit (T ble 6 and Fig. 1). This was 5.8 f the newborn infants hospitalized, and their distribution over the studied period wa fairly even They ll were over 2 days ld on admission and only 2 of them had been sent to the surgical unit immediately from the newborn nurseries of different hospit ls, while 4 had been transferr d from arious other units of the same hospital

A later finding of *Pseudomonas* was made in 20 infants in 19 of all inf nts admitted as newborn In most cases these patients had arrived directl from newborn nurseries and only 2 had been transferred from other hosp tal un t Samples had not been taken on admission from 4 patients, ? of whom w re under tre tment d ring the first 3 months of this study

The number of newborn infants who had become colonized with *Pseudomonas* while in the surgical unit was highest during the first 3 months f this study these 15 patients made up over a th rd of ll the newborn in the unit at the time During the remainder of the studied period only 7 (10 %) f those admitted as newborn became colonized while in the unit. The difference in the incidences between the tw periods is highly significant.

Various factors influencing colonization. The number of *Pseudomonas*-colonized newborn girls wa over twofold that f newborn boys, whereas the total series of 104 newborn nf nts contained 2 boy more than girls (Table 7) About a fifth f the colonized and bout tenth of the non-colonized neonates were in the praemature weight range. The highest incidence of *Pseudomonas* colonization was seen among the newborn

TABLE 6 *T me f diagnosis of P u d m n colonization in the neonat patients during the f rst 3 months and the follow ing 9 month of the present study*

	Oct. 1 – Dec 31 1962	Jan. 1 – Sept 30, 1963	Total
Pseudomonas colonized			
Coloniz tion diagnosed during the first 2 da in hospital	1	5	6 (5.8)
Colonization diagnosed later	15	7	20 (19)
Non-colonized	19	59	8
Total number of neonate pa ients	35	71	104

TABLE 7 *Relationship f P u d m n colonization to sex birthweight and presence of anomalies in the neonat patients.*

	Pseudomonas-colonized	Non-colonized	Total
Boys	8	45	53
Girls	18	33	51
Birth eight ov 2.5 kg	21	70	91
Birthweight 2 kg or less	5	8	13
Severe anomaly of the digestiv tract	20	24	44
Other anomaly	2	33	35
No anomal	4	21	25
Tw or more anomalies	11	11	22

of the washbasin drain in the patients waiting room. In the ward unit the *organism was isolated* in the first 3 months from edges of the kitchen sink drain and from a kitchen brush, from one incubator used for newborn patients, and from the mouth of the washbasin drain in four of the *patient rooms*. At the *very beginning* of the fourth month of investigation *Pseudomonas* cultures were obtained from glass bottles used for children's continuous drip-feeding

Pseudomonas organisms were obtained later only from bathtubs and washbasins in the isolation rooms of colonized children, in addition to which the kitchen sink *was again found to* be contaminated at the end of the investigation period.

The settling plates for collection of air borne bacteria did not yield any growth of *Pseudomonas*

Occurrence of *Pseudomonas* in Different Types of Patient Groups

The series of patients studied can be divided into three groups patients admitted as newborn at less than 28 days of age urological patients, and other patients. The 26 infants in the *Pseudomonas* series who were admitted as newborn made up nearly a half of the colonized patients. *There were 8 urological cases in the Pseudomonas* series. The remaining 19 colonized patients were of different ages and had been admitted for various reasons, forming no distinct group

Table 5 presents the monthly distribution of *all patients and of Pseudomonas*-colonized *patients* in each of the above groups

A Patients Admitted as Newborn

Occurrence of Pseudomonas colonization and relationship to mortality *Pseudomonas* colonization was found in 26 of the 104 neonate patients treated in the unit, or in 25 per cent (Table 5) The incidence among the newborn was particularly high in the first 3 months of the study when the organism was isolated from 14 of the 33 neonates under treatment. During the following 9 months, only 12 of the 71 infants admitted as newborn were found to be colonized. The difference between these figures is statistically significant.

Deaths in the group of *Pseudomonas*-colonized infants who had been admitted as newborn totalled 13 9 occurring during the first 3 months

TABLE 5 *Number of neonate urological and other patients treated in the paediatric surgical unit and occurrence of Pseudomonas colonization in each group by months*

Year	1962			1963									
Month	Oct.	Nov	Dec.	Jan.	Feb.	Mar	Apr	May	June	July	Aug	Sept.	Total
Neonate patients	12	9	12	8	5	7	11	9	6	11	7	7	104
of whom *Pseudomonas*-colonized	6	4	6	0	0	2	4	0	1	1	2	2	26
Urological patients	5	1	1	2	2	1	1	0	1	0	3	5	22
of whom Pseudo*monas*-colonized	3	1	0	0	1	1	0	0	0	0	1	1	8
Other patients	39	35	32	41	50	24	29	29	32	33	28	37	387
of whom *Pseudomonas*-colonized	1	2	2	1	0	3	0	0	2	0	2	6	19
Total number of patients	56	45	45	51	57	32	41	38	39	44	38	49	513
of whom *Pseudomonas*-colonized	9	7	7	2	1	5	4	0	3	1	5	9	53

and 3 during the last 2 months of this study Among the 78 non-colonized newborn there were 16 deaths, which were fairly e enly distributed over the study period.

Time of colonization. *Pseudomonas* bacilli ere found in 6 neonates during the first 2 days in the surgical unit (T ble 6 and Fig. 4) This was 5.8 of the newborn infants hospitalized, nd their distribution over the studied period was fairly even. They all were over 2 days old on admission, and only 2 of them had been sent to the surgical unit immediatel from the newborn nurseries of different hospitals, while 4 had been transferred from arious other units of the same hospital

A later finding f *Pseudomonas* w made in 20 inf nts, in 19 f all infants admitted newborn I most cases these patients had arrived directl from newborn nurseries and only 2 had been transferred from other hosp tal units Samples had not been taken on admission from 4 patients, 2 f whom were under treatment during the first 3 months of thi study

The number of newborn infants who had become colonized with *Pseudomonas* while in the surgical unit was highest during the first 3 months f this study these 13 patients made up over a third f all the newborn in the unit at the time. During the remainder f the studied period only 7 (10 %) of those admitted as newborn became colonized while in the unit. The dif ference in the incidences between the tw periods i h ghly significant

Various factors influencing colonization. The umber of *Pseudomonas*-colonized newborn girls w over twofold that f newborn boys, whereas the total series of 104 newborn infants contained 2 boys more than girls (Table 7) About a fifth of the colonized and bout a tenth f the non-colonized neonates were in the praemature weight range. The highest incidence of *Pseudomonas* colonization was seen mong the newborn

TABLE 6 *T me f diagnosis of P u d m colonization in the neonat patients during the f rst 3 months and the following 9 months f th present study*

	Oct. 1 – Dec. 31 1962	Jan. 1 – Sept. 30, 1963	Total
Pseudomonas colonized			
Colonization diagnosed during the first 2 da in hospital	1	5	6 (5.8)
Colonization diagnosed later	13	7	20 (19)
Non-colonized	19	59	78
Total number of neonate pa ie ts	33	71	104

TABLE *Relationsh p of P u d m n colonization t sex birthweight and presence f anomalies in the neonat patients*

	Pseudomonas-colonized	Non-colonized	T tal
Boys	8	45	53
Girls	18	33	51
Birthweight over 2.5 kg	21	70	91
Birthweight 2.5 kg or less	5	8	13
Severe anomaly of the digesti tract	20	24	44
Other anomaly	2	33	53
No anomal	4	21	23
T or more anomalies	11	11	22

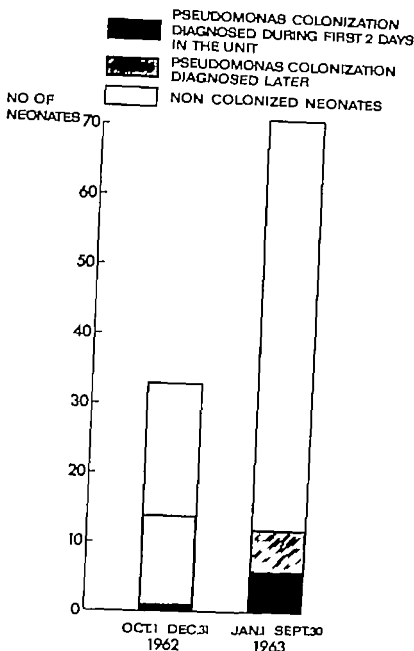


Fig 4 Time of d agnosi f Pseudomonas colonization in patients adm tted as newborn during th f rst 3 months and t follow ing 9 ont f th present study

infants who were undergoing operation for severe anomaly of the digestiv tra t, almost half of them yielding cultu es of the organism

The following conditions were regarded as severe digestive tract anomalies oesophageal atresia or stenosis of the mall intestine, ruptured mphalocele, and severe Hirschsprung s disease Apart from minor anal anomalies, there were only 2 cases of true atresia of the anus, and *Pseudomonas* was not found in any of these 10 patients. A very h gh frequency of col nization was f und among newborn infants operated on for oesophageal atresia they mad up half of the lonized newborn, and o a half f the patients with oesophageal atresia ere infected w th *Pseudomonas* (Table 8) The numbe f colonized pa tients w th atresia of the oesophagus diff rs h gl ly significantly from the umber of other colonized neonates, whereas the difference in number between colonized patients w th inte-

TABLE 8. *Distribution of the neonatal patients by diagnosis, and occurrence of Pseudomonas colonization in each diagnosis group*

Diagnosis	Pseudomonas-colonized	Non-colonized	Total
Atresia oesophagi	13	10	23
Fistula oesophagotrachealis	1	0	1
Atresia seu stenosis duodeni, ilei	4	10	14
Omphalocele rupturata	1	4	5
Mb Hirschprung	1	0	1
Atresia seu anomaliae ani	0	10	10
Malrotatio	0	2	2
Stenosis pylori	2	6	8
Hernia diaphragmatica	0	5	5
Pneumothorax	1	1	2
Hydrocephalus	1	3	4
Pes equinovarus	1	6	7
Other operated patients	0	15	15
Patients under examination	1	6	7
Total number of neonate patients	26	78	104

tinal atresia and other colonized neonates was not significant

Relationship between Pseudomonas colonization and length of hospitalization. The newborn infants with oesophageal or intestinal atresia or with omphalocele formed a fairly uniform group with respect to type of treatment and prognosis but the average length of hospitalization of the *Pseudomonas*-colonized infants was longer than that of the non-colonized. In the case of 20 colonized newborn it was 34 days (range 3–144 days) while for 24 non-colonized newborn it was 18 days (range 1–54 days). The length of hospitalization was less than 18 days the case of 8 infants who died in the colonized group and of 6 who died in the non-colonized group. When these lost days of treatment are included the average length of hospitalization of colonized neonates was 50 days and that of non-colonized 22 days. The difference has no statistical significance because of the wide dispersion of the number of days in hospital in the group of *Pseudomonas*-colonized neonates.

Pseudomonas infections. In the group of infants admitted to the surgical unit as newborn, 17 of the 26 found to be colonized with *Pseudomonas* had symptoms of infection (Table 9). Ten of these children were under treatment in the first 3 months of the present study and all 10 became colonized with *Pseudomonas* and developed symptoms during hospitalization. In the following 9 months symptoms of *Pseudomonas* infection were seen in 7 newborn, 3 of whom were found to have the infection already on admission.

The most common symptom was pneumonia, which was diagnosed in 10 infants. Six of these cases occurred during the first 3 months of this study. The diagnosis was based in 6 cases on cultures of bronchial mucus and clinical symptoms of pneumonia during life, and in the other cases on autopsy findings alone. Autopsies revealed also 3 cases of bronchitis, all of them during the first 3 months.

The manifestation next in frequency was focal infection. Wound infection occurred in 5 patients, 4 of whom were treated in the first 3 months. Two patients had several suppurating wounds, and in 4 cases suppuration caused dehiscence of the wound. In 2 cases the cultures from pus yielded also other bacteria, but *Pseudomonas* was predominant. Conjunctivitis occurred in 3, um-

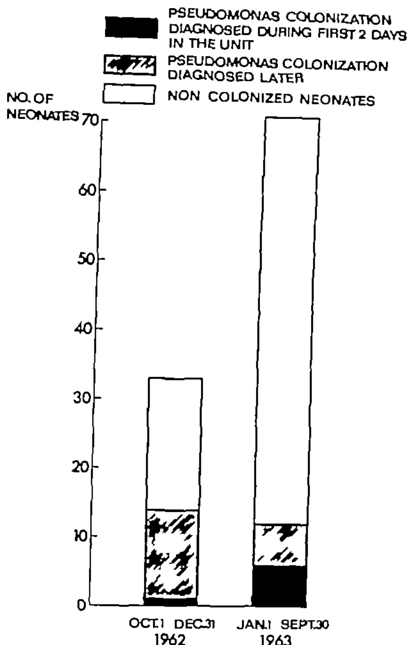


Fig 4 Time f d agnosis f P eudomonas colon ation in patients adm tted as newborn during the first 3 months and the following 9 n ontl of the present study

infants who were undergoing operation for evere anomaly of the digestive tract, almost half of them yielding cultures of the organism.

The following conditions were regarded as vere digestive tract anomalies oesophageal atresia or stenosi of the s nall ntestine, ruptured mphalocele and se ere H rschsprung s disease Apart from m or anal anomalies, there were only 2 cases of true atresia of th anus, and *Pseu domonas* was not found in a y of these 10 patients. A very high frequency of colonization was found among newborn infants operated on for oesophageal atresia they ma le up half of the colonized newborn and over a half of the patient with oesophageal atresia were infected with *Pseu domonas* (Table 8) The number of colonized pa tients th atresi of the oesopl gus differs highly signif cantly from the number of other colonized neo ates, whereas th diff rence n nun ber between colonized pat ts with ntes

TABLE 10. *Relationship of mortality to Pseudomonas colonization and to inflammatory changes observed at autopsy in the neonate patients during the first 3 months and the following 9 months of the present study*

	Oct. 1 – Dec. 31 1962			Jan. 1 – Sept. 30, 1963			Total		
	Pseudomonas-colonized	Non-colonized	Total	Pseudomonas colonized	Non-colonized	Total	Pseudomonas-colonized	Non-colonized	Total
Total number of neonate patients	14	19	33	12	59	71	26	78	104
Number of deaths	9	5	14	4	11	15	13	16	29
Finding of infection at autopsy	7	2	9	4	3	7	11	5	16

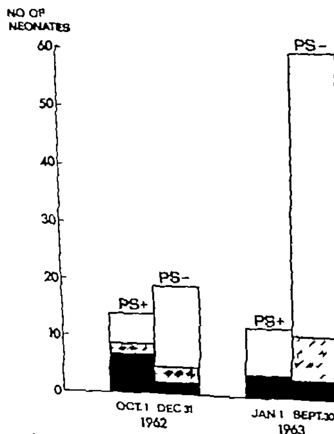


Fig. 5. Relationship of mortality to Pseudomonas colonization and to autopsy findings of infection in patients admitted as newborn during the first 3 months and the following 9 months of the present study

TABLE 9 *Various forms of Pseudomonas infection occurring among the neonate patients during the first 3 months and the following 9 months of the present study*

	Oct. 1 – Dec 31 1962	Jan. 1 – Sept. 30, 1963	T t l
Total n mbe of patients admitted as newborn	33	71	104
Number of *Pseudomonas*-colonized	14	12	26
Number w th symptoms f *Pseudomonas* infection	10	7	17
Sy uptoms evident on admission	0	3	3
Clinical picture			
Pn umonia	6	4	10
Bronchitis	3	0	3
Septicaemi	1	0	1
Peritonitis	3	0	3
Wound infection	4	1	5
Umbilical infection	2	0	2
Conjuncti tis	1	2	3
Urinary tra t infection	1	0	1
Abscess	0	1	1

Pseudomonas was consid red t be th infect agent when def te local symptoms f i fection were supported by a bact rial culture from th site of infection, in which *Pseudomonas* w the predominant micro-organism. The diagnoses f periton tis, septicaemia, bro ch it and f 4 cases of pneumonia were based n the findings at utopsy

bilical stump infection in 2, and a cutaneous abscess at the site of medical injection in one newborn.

Peritonitis was diagnosed in 3 infants who underwent laparatomy during the first 3 months studied All of them had symptoms of peritonitis during life, bacterial cultures made from the faeces in 2 of the cases yielded *Pseudomonas*, and autopsy showed in all 3 cases distinct peritonitic changes, greenish pus in the abdominal cavity and *Pseudomonas* growing from cultures of samples from the lungs.

A case of septicaemia verified at autopsy occurred in the first 3 months, when there also was a case of urinary tract infection due to *Pseudomonas* in a pre iously catheterized infant.

The 29 newborn admissions who died d ring the studied period included 11 of the 17 infants with a *Pseudomonas* infect on. Only one patient with pneumonia recov red from the infection of the other infected patients who recovered 2 h d had conjunctivitis and one patient each had had skin abscess, wound infection and urinary tract infection

Autopsy findings of colonization and infection with Pseudomonas Cultures of lung samples taken at the autopsies of 29 infants who had been admitted to the surgical unit as new born showed growth of *Pseudomonas* in 13 cases (Table 10 and Fig 5) Histological evidence of infection was found in 11 of these infants, while such changes were present in only 5 of the 16 infants whose lung culture at autopsy d d not yield *Pseudomonas* Thus the incidence of infection in the former group was twofold in comparison to the latter group

Details of the 13 cases with *Pseudomonas* in the lung samples are presented in Table 11 All the infants w re under 28 days of age when admitted and when the first signs of *Pseudomonas* infection becam manifest, though at the ti e of deatl tl oldest child was aged 5 months.

The typical present ng sympt ptom the general ympt ms stated n the lit rat re period of subnormal temperature an indef n te poor condition, abdominal d stention and omiting respir t ry diff culties of various kinds, cyanos

TABLE 10. *Relationship of mortality to Pseudomonas colonization and to inflammatory changes observed at autopsy in the neonat patient during the first 3 months and the following 9 months of the present study*

	Oct. 1 – Dec. 31 1962			Jan. 1 – Sept. 30, 1963			Total		
	Pseudo-monas-colonized	Non-colonized	Total	*Pseudo-monas-colonized*	Non-colonized	Total	*Pseudo-monas-colonized*	Non colonized	Total
Total number of neonate patients	14	19	33	12	59	71	26	8	104
Number of deaths	9	5	14	4	11	15	13	16	29
Finding of infection at autopsy	7	2	9	4	3	7	11	5	16

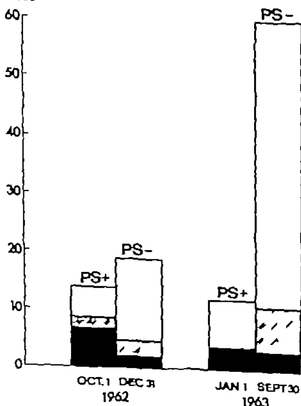


Fig. 5. Relationship of mortality t P d m colonization and to autopsy findings of in,ection in patients admitted as newborn during the first 3 months and the following 9 months of the present study

TABLE 11 *Diagnosis symptoms Pseudomonas culture and autopsy findings in Pseudomonas-colonized neonatal patients who died during the period of study*

Case No.	Sex Age on admission Birthwt	Basic disease	*Pseudomonas* culture findings	Symptoms	Days in unit	Autopsy findings	Bacterial finding from lung
196_							
1	Female 9 hr 3,000 g	Atresia oesophagi fistula Ductus arteriosus apertus	At 3 weeks throat, nose Ps+++ later bronchial mucus and wound pus	Recurring pneumonia, wounds suppurate thrombopenia cardiac insufficiency	135	Bilat. pneumonia, abscesses at wound margins patent ductus arteriosus	*Pseudomonas*
2	Male 3 ds 4,060 g	Mb. Hirschsprung	At weeks throat, nose Ps+++ later faeces, wound pus, eye discharge	Ileus, blood and mucus in faeces, wounds suppurate conjunctivitis, subnormal temperature thrombopenia	37	Peritonitis, greenish pus in abdomen, bilat. pneumonia, septicaemia	*Pseudomonas* *Klebsiella*
3	Female 5 hr _650 g	Omphalocel rupturatum	At under 4 weeks throat Ps−++ later navel and faeces	Ileus, navel suppurates, subnormal temperature thrombopenia	5_	Peritonitis, greenish pus in abdomen purulent bronchitis, adrenal infection	*Pseudomonas* *Proteus vulgaris*
4	Male 20 ds 4,550 g	Hydrocephalus P rencephal	Culture not made	Subnormal temperature anaemic, terminal pneumonia	8	Diffuse partl purulent, bilat. pneumonia	*Pseudomonas*
5	Female ds 3,850 g	Atresia oesophagi fistula	On th postoperati da bronchial mucus P +++	Pneumonia, subnormal temperature	10	Bilat. diffuse pneumonia, right pleuritis, ruptured anastomosis	*Pseudomonas*
6	Male 36 hr 1,870 g	Atresia duoden Praematuritas	Throat and nose Ps −	On 3rd postoperati da subnormal temperature icterus, abdomen hard, blood and mucus in faces	5	Peritonitis, ulcerations in oesophageal mucous membrane, partial pulmonary atelectasis	*Pseudomonas*
	Female d 3,470 g	Atresia oesophagi Anus vestibul n Aplasia poll cis dx	Throat P + on admission	On admission lung changes, condition poor subnormal temperature icterus, distended abdomen	4	Diffuse haemorrhages in both lungs	*Pseudomonas*
8	Male 30 h 1,590 g	Atresia oesophagi et duodeni Mongolismus Praematuritas	Throat and nose Ps −	Condition conti nousl poo episodes of pnoea, subnormal temperature, icterus	3	Ulcerat bronchitis, bilat. bronchopneumonia	*Pseudomonas*

9	I male h 2,320 g	A sia oesophag … A us vestibulum Aplasia rad … Pneumatu as	Throa … nd I fal … acu Ps	… on … pneu episode f apno … pneumon subnormal temperat re	+	Aspiration pneumonia	Pseudomonas
1963 10	Female 6 h 1,800 g	A esia oesophag fistula I meconial …	Throat and nose Ps –	On 2nd postoperat da sclerodema, … subnormal temperat pneumonia	+	B l t pneumonia, right pleurit s, ruptured anastomosis	Pseudomonas
11	Female 9 da 2,610 g	Atresia oesophag Ductus arteriosus pertus	On 4th postoperati da bronchial mucus Ps+ + + later throat and nose	Ileus, subnormal temperat re pneu monia	11	Bilat. bronchopneumonia and haemorrhages, anastomos rupt red, patent ductus arteriosus	Pseudomonas
12	I male 17 da 2,950 g	I st la oesophago-racheal … um …	On adm sion throat nose and bronchial mucu Ps+ + +	Immediat l fter operation pneumonia, fluctuating temperat re card ac insufficiency	11	B lat. diffuse pneumon … … and anomalous pulmonary …	Pseudomonas
13	Male 1 d 3,000 g	Atresia oesophag fistula	On 3rd postoperati da bronchial mucus nd wound pus Ps+ + +	On 2nd postoperati day pneumonia wound suppuration, scleroedema, episodes of apnoea	+	B l t pneu onia, right pleuritis; rupt red anastomosis	Pseudomonas Unidentified gram negati bacillus

and ttacks f apnoea (22, 39, 40, 50, 72) The faeces f patients with peritonitis were loose and slimy and at some stage blood-stained. Thrombopenia was found in 3 patients in most cases the count was not made. Anaemia was present in all protracted cases. Leucocyte counts arying from high to low were seen. Three patients were unusually hea ily icteric and 2 had scleroderma.

Since special ttention had not been paid in the first histological examination to changes typical f *Pseudomonas* infection, the lung samples from all f the 15 *Pseudomonas*-colonized newborn infants who died were re-examined. The specimens were stained by the an Gieson and haematoxylin methods.

The following were regarded as characteristic changes in *Pseudomonas* pneumonia

A. Haemorrhagic necroses associated with vasculitis and or thrombi in the walls of small and medium-sized pulmonary muscular arteries.

B. Necrotic *granulomata with haemorrhagic* margins in association with the ascular changes. In connection with the changes here described, ttention was paid to the presence of histologically demonstrable bacteria and absence f inflammatory cell reaction (39 40, 52).

Specific changes of this kind were found in only 3 f the re-examined cases. The changes consisted of haemorrhagic necroses and vasculitis an *additional finding f* bacteria was made in 2 cases only These 3 patients were cases 5, 10 and 15. Their detailed case reports, as well as those of 3 other patients, cases 1 3 and 11 are given below

Case 1

A girl born on May 17 1962 after a normal pregnancy and uneventful deli *ery birthweight* 3,000 g and Apgar score 7–9 was admitted t the age f 9 hours because of atresia of the oesophagus.

On admission she was in good condition and oesophago-oesophagostomy by *right* thoracotomy was immediately done. Her immediate postoperati condition was good and prophylaxis with

TABLE 11 *Diagnosis symptoms Pseudomonas culture and autopsy findings in Pseudomonas-colonized neonate patients who died during the period of study*

Case No	Sex Age on admission Birthwt	Basic disease	*Pseudomonas* culture findings	Symptoms	Days in unit	Autopsy findings	Bacterial finding from lung
1962							
1	F male 9 h 3,000 g	Atresia oesophagi fistula Ductus arteriosus apertus	At 3 weeks throat, nose Ps+++ later bronchial mucus and wound pus	Recurring pneumonia, wounds suppurate, thrombopenia cardiac insufficiency	135	Bilat. pn umonia, abscesses at w und margins patent ductus arteriosus	*Pseudomonas*
2	Male 5 ds 4,000 g	Mb Hirschsprung	At 3 weeks throat, nose Ps+++ later f eces, wound pus, eye discharge	Ileus, blood and mucus in faeces, wounds suppurate, conjuncti itis, subnormal temperature thrombopenia	37	Peritonitis, greenish pus in abdomen, bilat. pneumonia, septicaemia	*Pseudon onas Klebsiella*
3	Femal 5 hr 2,650 g	Omph locele rupturatum	At under 4 weeks throat Ps+++ late na el and faeces	Ileus, na el suppurates, subnormal temperature, thrombopeni	52	Peritonitis, greenish pus in abdomen purulent bronchitis, adrenal infection	*Pseudomonas Proteus vulgaris*
4	Male 20 ds 4,550 g	H drocephalus Porenceph lia	Culture not made	Subnormal temperature, anaemic terminal pn monia	8	Diffuse, partly purulent, bilat. pneumonia	*Pseudomonas*
5	Female 2 ds 3,850 g	Atresia oesophagi f stul	On 4th postoperati d y bronchial mucus P +++	Pneumonia, subnormal temperature	10	Bilat. diffuse pneumonia, right pleuritis, ruptured anastomosis	*Pseudomonas*
6	Mal 36 hr 1,8?0 g	Atresia duoden Praematuritas	Throat nd nose P –	On 3rd postoperati day subnormal tem perat re, icterus, abdomen hard, blood and mucus in f ces	5	Peritonitis, ulcerations in oesophageal mucous membrane, partial pulmonary atelectasis	*Pseudomonas*
7	Female 2 ds 3,420 g	Atresia oesophagi A us est bulari Aplasia pollici dx	Throat P + on admission	On admission lung changes, cond tion poo subnormal temperat icterus, distended bdomen	4	D ffuse haemorrhages in both lungs	*Pseudomonas*
8	M l 36 h 1,590 g	Atres oesophagi t duoden Mongolismus Praemat rita	Throat and nose Ps –	Cond tion continuously poo episodes f pnoea, subn rmal temperature, cteru	5	Ulcerati bronchitis, b l t. bronchopneumoni	*Pseudomonas*

	I ew le 7 hr 2,520 g	A sia oesophagi f la A os subalare Aplasia radi Praema rius	Th a ose and bronchial us Ps –	Candi ion en mucoid prior episodes f apnoea pneumonia subnormal tempera re	I	Asp ra ion pneumonia	*Pseudomonas*
1963 10	Female 6 hr 1,800 g	At sia oesophagi fist l Praematuri as	Throat and nose Ps –	On 2nd postoperat da scleroedema, icterus, subnormal emperature pneumonia	4	B lat pneumonia, right pleuritis, ruptured anastomosis	*Pseudomonas*
11	Female 2 da 2,640 g	Atresia oesophagi Ductus arteriosus apertus	On th postoperativ d y bronchial mucus Ps+++ later throat and nose	Ileus, subnormal temperat re pneumonia	11	Bilat. bronchopneumonia and haemorrhages, anastomosis ruptured; patent ductus arteriosus	*Pseudomonas*
12	Female 17 da 2,950 g	F stula oesophago-trachealis V trum cordis cong	On admission throat, nose and bronchial mucus Ps+++	Immediately after operation pneumonia, fluctuating temperature cardiac insufficiency	11	Bilat. d ffuse pneumonia; coarct tion f aort and nomalous pulmonary eins	*Pseudomonas*
13	Male 1 d 3,000 g	Atresia oesophagi fistula	On 3rd postoperativ da bronchial mucus nd wound pus Ps+++	On 2nd postoperati day pneumonia, wound suppurates, scleroedema, episodes f pnoea	I	Bilat pneumonia, right pleuritis; ruptured anastomosis	*Pseudomonas* U identified gram-neg ti bacillus

and ttacks f pnoea (22, 39 40, 55, 72) The faeces f patients w th peritonitis were loose and slimy and t some stage blood-stained. Thrombopenia was found in 3 patients in most cases the count was not made. Anaemia was present in all protracted cases. Leucocyte counts arying from high to low were seen. Three patients were unusually hea ily icteric and 2 had scleroedema.

Since special ttention had not been paid in the first histological xamination to changes typical f *Pseudomonas* nfection, the lung samples from all f the 13 *Pseudomonas*-colonized newborn inf nts who died were re-exam ined. The specimens were stained by the an Gieson and haematoxylin methods.

The following were regarded as characteristic changes in *Pseudomonas* pneumonia

A. Haemorrhagic necroses associated with vasculitis and/or thrombi in the walls f small and medium-sized pulmonary muscular arteries.

B. Necrotic granulomata with haemorrhagic margins in association with the ascular changes. In connection with the changes here described, ttention was paid to the presence f histologically demonstrable bacteria and absence of inflammatory cell reaction (39 40, 52).

Specific changes f this kind were found in only 3 of the re-examined cases. The changes consisted of haemorrhagic necroses and vasculitis an additional finding f bacteria was made in 2 cases only These 3 patients were cases 5, 10 and 13. Their detailed case reports, as well as those f 3 ther patients, cases 1 3 and 11 are gi en below

Case 1

A girl born on May 17 1962 after a normal pregnancy and unevential deli ery birthweight 3,000 g and Apgar score 7–9, was admitted at the age f 9 hours because of tresia of the oesophagus.

On admission she was in good condition and oesophago-oesophagostomy by right thoracotomy was immedi tely done. Her immediate postoperati condition was good and prophylaxis with

TABLE 11 *Diagnosis symptoms, Pseudomonas culture and autopsy findings in Pseudomonas-colonized neonate patients who died during the period of study*

Case No	Sex Age on admission Birthwt.	Basic disease	*Pseudomonas* culture findings	Symptoms	Days in unit	Autopsy findings	Bacterial finding from lung
1962							
1	Female 9 h 3,000 g	Atresia oesophagi f stula Ductus arteriosus apertus	At 3 weeks throat nose Ps+++ later bro chial mucus and w und pus	Recurring pneumonia, w unds suppurate, thrombopenia card ac insufficiency	155	Bilat. pneumonia, bscesses t wound margins patent ductus arteriosus	*Pseudomonas*
2	M l 3 ds 4,060 g	Mb Hirschsprung	At 3 weeks throat, nose Ps+++ l ter f eces, wound pus, ey discharge	Ileus, blood and mucus in faeces, wounds suppurate, conjunctivitis, subnormal temperature, thrombopenia	37	Periton tis, greenish pus in abdomen, bilat. pneumonia, septicaemia	*Pseudomonas* *Klebsiella*
3	Female 5 h 2,650 g	Omph locel rupturatum	At unde 4 weeks throat Ps+++ late na l and f eces	Ileus, na el suppurates, subnormal temperature, thrombopenia	52	Peritonitis, greenish pus in abdomen purulent bronchitis, drenal infection	*Pseudomonas* *Proteus vulgaris*
4	M le 20 ds 4 550 g	H drocephalus Porencephal	Culture not mad	S bnormal temperature, anaemic, terminal pneumonia	8	D ffuse, p rtly purulent, bilat. pneumonia	*Pseudomonas*
5	Female 2 d 3,850 g	Atresi oesophag e. fistul	On 4th postoperat ve day bronchial mucus P +++	Pneumonia, subnormal temperature	10	Bilat. d ffuse pneumonia right pleuritis, ruptured nastomosis	*Pseudomonas*
6	M le 36 hr 1,870 g	Atresi duodeni Praem turitas	Throat and nose Ps –	On 3rd postoperati d y subnormal tem perat re, icterus, bdomen h rd, blood and mucus in faces	5	Periton tis, ulcerations in oesophageal mucous membrane, partial pulmon ry atelectasis	*Pseudomonas*
7	Female 2 ds 3 420 g	Atresi oesophagi An estib lari Aplasia poll ci d	Throat Ps + on dmission	O dmission lung hanges, ond tion poo subnormal temperature icterus, distended bdomen	4	D ffuse haemorrl ges in botl lung	*Pseudomonas*
8	Male 36 h 1,590 g	Atresi oesophag t duoden Mong l smus Praem t ritas	Throat nd nose Ps –	Cond tion continuously poo episodes f p oea, subnormal t mperat re, icteru	3	Ulc rati bronchitis, bil t bro chop eumonia	*Pseudomonas*

showed anaemia and thrombopenia, with haemoglobin 9.5 g/100 ml and thrombocyte count 27,500. Treatment consisted of polymyxin in a daily dose of 3 mg/kg, gamma-globulin and, because of her extremely poor condition, cortisone. There was some improvement, but with persisting symptoms of paralytic ileus. She could not manage without cortisone, every attempt to discontinue administration being followed by rapid deterioration of her general condition. *Pseudomonas* was continuously the predominant organism from the throat, faeces and suppurating umbilicus. Polymyxin administration was followed by kanamycin and colistin and there seemed to be gradual improvement. At the age of 8 weeks, when she had been without cortisone for days, her general condition suddenly deteriorated and she died within few hours.

Autopsy revealed foci of purulent bronchitis but in the lungs there were no signs of pneumonia or changes specific for *Pseudomonas*. This organism and *Proteus vulgaris* grew from lung samples. Abundant blue-green pus with the characteristic Pseudomonas odour was found in the abdominal cavity. The peritoneum was dull and covered with fibrinous blue-green membrane. The intestine was slightly enlarged and covered with numerous fibrinous membranes and adhesions of bluish green-yellow colour. The medulla of the left adrenal gland was partly blue-green and microscopic examination showed a necrotizing inflammation with bacteria and haemorrhagic foci.

daily bronchial toilettes were necessary because of profuse mucus. Prophylactically administered antibiotics were oxytetracycline, streptomycin and penicillin. Sample of bronchial mucus taken one day after operation showed no growth of bacteria, but *Pseudomonas* grew from a sample on the fourth day. At the same time there were roentgenological changes in the right lung, interpreted to be atelectasis and pneumonic infiltration. The child was icteric and had respiratory difficulties. Leucocyte and thrombocyte counts were not made at this stage. On the eighth postoperative day there was a sudden worsening in her general condition, with subnormal temperature, cyanosis and shadow throughout the right lung in the roentgenograms. On the suspicion of rupture of the anastomosis she was once more thoracotomized and gastrostomy was done. After the operation the child did not breathe spontaneously and she died at the age of nearly 12 days.

At autopsy a rupture was found in the posterior wall of the oesophagus at the site of the anastomosis. There was milk in the pleural cavity on the right side. The bronchial mucous membranes were reddish and contained slimy purulent discharge. Both lungs showed diffuse pneumonia and the right lung had an area of haemorrhagic necrosis adjacent to the pleura, with very slight inflammatory cell reaction at the margins. Bacteria were found at the margins of the necrotic area. There was vasculitis of the subpleural vessels. *Pseudomonas* grew from lung samples.

Case 5

The patient, a girl born on October 6, 1962, was nearly 2 days old when admitted because of oesophageal atresia. Pregnancy and delivery had been normal and her birthweight was 3,850 g and Apgar score 9.

She was in good condition on admission and oesophago-oesophagostomy by right thoracotomy was immediately performed. Moderate tenseness remained at the site of the anastomosis. Her immediate postoperative condition was good, but

Case 10

A girl born April 8, 1963 was admitted at the age of 6 hours because of atresia of the oesophagus. The mother had had toxaemia of late pregnancy and a normal delivery had taken place 10 days before the calculated term. The child weighed 1,800 g and received 10 Apgar points.

On admission her general condition was good and thoracotomy and oesophago-oesophagostomy were immediately performed. Cultures from nose

penicillin, streptomycin, chloramphenicol and tetracycline was instituted. At the age of 3 weeks there was an onset of respiratory difficulty and the first pharyngeal sample then taken gave a pure culture of *Pseudomonas*. When she was 4 weeks old pneumonia was diagnosed in the right lung and *Pseudomonas* grew from a sample of bronchial mucus. There were respiratory difficulties and subnormal temperature. Leucocyte counts were repeatedly less than 15 000 and thrombocytes were low in number". She received 2 mg/kg of polymyxin daily for eleven days. *Improvement occurred during treatment* and bacterial cultures became negative for *Pseudomonas*. Mild symptoms of cardiac insufficiency that had appeared at *the same time disappeared* with digitalization.

The child's weight gain was nevertheless not satisfactory and she was vomiting continually. Pyloromyotomy was therefore performed when she was 8 weeks old. Two days after operation a diagnosis of pneumonia of the right lung was again made and a bronchial mucus culture yielded *Pseudomonas*. Treatment was resumed with polymyxin and tetracycline, but discharge of mucus continued to be profuse and *Pseudomonas* was dominant in the nose and throat flora although the other symptoms disappeared. At the pneumonia stage there had again been *cardiac insufficiency which was kept under* control with digitalis. At this time the heart symptoms pointed to a patent ductus arteriosus.

At 11 weeks of age she again had pneumonia, now probably due to *Klebsiella* which was ob*tained as pure cultures from* the throat and nose. There was leucocytosis up to 41 000. She was given a short treatment with kanamycin and gamma globulin with some improvement, but the vomiting persisted and her weight did not increase. A hiatal hernia that had been diagnosed was considered responsible for the vomiting, and when the child was 15 weeks old fundus plication, gastropexy and gastrostomy were performed. Postoperatively she again had pneumonia and cardiac insufficiency. Throat *and nose cultures* yielded *Pseudomonas* and *Klebsiella* and the blood picture showed leucocytosis up to 51 000.

The operation wound began to suppurate, dehisced, was resutured, and opened once more. *Pseudomonas* was constantly the predominant organism in the wound pus, *Klebsiella* and other gram negative bacilli being present variably. Treatment consisted of sulfa, chloramphenicol, streptomycin and gamma globulin. The lung symptoms abated again and the cardiac insufficiency was kept under control with continuous digitalization but the vomiting persisted, body weight did no increase and the wound continued to suppurate. The infant died at the age of 19 weeks following a febrile period of 3 days with no additional symptoms.

At autopsy the state of the oesophagus was *found to be good. Small* pneumonic foci were seen under the microscope in a few areas of the lung but alterations specific for *Pseudomonas* were not found. A number of abscesses were seen by microscope in the dermis at the margins of the operation wound. The heart was normal with the exception of a patent ductus arteriosus.

Case 3

This full term girl, born after a normal pregnancy on September 23, 1962, had a ruptured omphalocele. Her birthweight was 2,650 g and Apgar score 9–10, and the delivery had been normal.

She was admitted 5 hours after birth in good condition, but had a mass of intestinal loops beside the navel. At an immediately undertaken operation the intestine was repositioned but considerable tension of the muscles remained.

Her general condition was good after the operation and she received tetracycline, chloramphenicol and streptomycin as prophylaxis. Intestinal passage was still poor, apparently due to peritonitis, and she received continually part of *her food parenterally*. When the child was nearly 4 weeks of age a dramatic deterioration occurred in her condition, with cyanosis, subnormal temperature and abdominal distention. The throat sample yielded a pure growth of *Pseudomonas*. The blood picture

for the pleural suction tube began to suppurate and Pseudomonas and a gram-negative bacillus of the Klebsiella group grew from the pus. On the fourth postoperative day the child was very poor, scleredemic and had intermittent periods of apnoea. He died 4 1/2 days after operation. The thrombocytes had not been examined; the leucocyte count on the day of death was 8,800. Penicillin and streptomycin had been administered as prophylactic antibiotic treatment, throughout the time of hospitalization.

At autopsy the oesophageal anastomosis was found to have partially opened and there was pus in the adjacent part of the mediastinum. The pleura on the right side had a fibrinous covering, the air content was reduced in both lungs and pus oozed from the lung tissue on compression. There also was pus in the bronchi. Histological examination showed in both lungs pneumonic changes and a number of foci of haemorrhagic necrosis, and in the small arteries partially obstructing vasculitis. At the margins of the necrotic areas there were bacteria but only slight inflammatory cell reaction. Lung sample cultures yielded Pseudomonas and an unidentified gram-negative rod bacillus.

Neonates with Oesophageal Atresia. Among the 76 *Pseudomonas*-colonized newborn infants the largest uniform group was comprised of the 13 patients with atresia of the oesophagus and one patient with tracheo-oesophageal fistula (Table 8). Nearly two-thirds of the 24 patients treated in the unit for oesophageal atresia during the period of this study were *Pseudomonas*-colonized.

Mortality in the group of 24 neonates with oesophageal atresia during the period was 15 patients, or over half of these patients (Table 12). None of those who died were *Pseudomonas* colonized. At autopsy pneumonia was confirmed in 7 of the latter whereas it was present in only one of the 4 non-colonized infants with oesophageal atresia who died.

In Table 12 the patients with oesophageal atresia are distributed into groups that have significance from the point of prognosis (58, 171). The correlations between these groups and *Pseudomonas* colonization, mortality and autopsy finding of pneumonia are presented.

Two of the newborn patients who on admission were in good general condition graded as A died 10 and 4 days after operation. In both cases pseudomonal pneumonia was diagnosed during

TABLE 12. *Condition on admission of neonates with oesophageal atresia and relationship to Pseudomonas colonization, mortality and autopsy finding of pneumonia.*

	Pseudomonas-colonized			Non-colonized			Total		
	No. of cases	No. of deaths	Pneumonia	No. of cases	No. of deaths	Pneumonia	No. of cases	No. of deaths	Pneumonia
Group A Birthweight over 2.5 kg good condition	4	2	2	5	0	0	9	2	2
Group B Birthweight 1.8–2.5 kg good condition, or higher birthweight but child had also other anomalies or pneumonia	7	4	3	3	2	1	10	6	4
Group C Birthweight under 1.8 kg or higher but child had severe pneumonia or grave anomaly	3	3	2	2	2	0	5	5	2
Total number of patients with oesophageal atresia	14	9	7	10	4	1	24	15	[illegible]

and throat samples taken on admission were negative. Postoperative recovery was at first uneventful penicillin and streptomycin were given as prophylactic medication. Two days after operation her temperature fell suddenly to below 31°C and she became icteric and scleroedemic. Roentgenograms revealed slight changes in the right lung Blood examinations were not made at this time Cortisone was administered for the scleroedema. On the following day there were clear signs of rupture of the oesophageal anastomosis, pleural suction brought out food, and there were extensive roentgenological changes in the right lung. Gastrostomy was done on the same day following which the child died at the age of slightly over 4 days.

At autopsy the oesophageal anastomosis was found to have opened completely The surface of the right lung was covered with a green fibrinous coating. Histologically both lungs exhibited haemorrhagic areas and some haemorrhagic necrotic foci with diffuse margins, associated with obstructive vasculitis. No bacteria were found The necrotic areas showed hardly any inflammatory cell reaction. Bacterial cultures of lung samples yielded *Pseudomonas.*

Case 11

A girl born on August 15 1963 after a normal pregnancy was admitted at the age of 2 days because of atresia of the oesophagus. Delivery had been normal and her birthweight had been 2,640 g and Apgar score 10

The condition of the child was good on admission and oesophago-oesophagostomy through right thoracotomy was immediately performed.

Following the operation the child suffered from very profuse mucus in her airways and constant bronchial toilettes were necessary Antibiotic prophylaxis consisted of penicillin and streptomycin When she was 5 days old, gastrostomy was done because of vomiting. One day later roentgenograms showed mild pneumonic changes in both lungs and *Pseudomonas* grew in cultures of bronchial mucus. She had respiratory difficulties, a subnormal temperature and icterus. The haemoglobin, leucocyte and thrombocyte levels were normal. Feeding by gastrostomy tube was not successful, the child continually vomited and laparotomy was therefore done when she was 8 days old on the suspicion of pyloric stenosis. No obstruction to intestinal passage was found. The medication was supplemented with chloramphenicol. Her condition continued to deteriorate and the vomiting and abdominal distention persisted. When the child was 11 days old there were extensive roentgenological changes in the right lung and she died at the age of 12 days.

Autopsy revealed at the site of the anastomosis in the oesophagus a small rupture opening into the right pleural cavity The trachea contained blood-stained purulent exudate. Haemorrhagic areas were present in both lungs beneath the pleura. Fibrinous adhesions were seen on the pleural surface on the right. Histological examination of lung tissue showed numerous collapsed areas, and there were some leucocytes and haemorrhages here and there in the bronchi and alveoli Changes specific for *Pseudomonas* infection were not found. Lung sample cultures showed growth of *Pseudomonas.* An additional finding was a patent ductus arteriosus.

Case 13

This patient was a boy born on September 6 1963 after a normal pregnancy Birthweight was 3 000 g and the Apgar score 9–10 He was 1 day old when admitted because of atresia of the oesophagus.

On admission he was in a good condition and oesophago-oesophagostomy through right thoracotomy was performed at once Samples of nose throat and bronchial mucus taken at the time of admission were negative for *Pseudomonas*

His immediate postoperative state was good, but 2 days later rales were audible over the lungs and he had respiratory difficulties. Sample of bronchial mucus taken 3 days after operation gave pure culture of *Pseudomonas.* The opening

for the pleural suction tube began to suppurate and *Pseudomonas* and a gram-negative bacillus of the *Klebsiella* group grew from the pus. On the fourth postoperati day the child was ery poor scleroedemic and had intermittent periods of apnoea. He died 4 1/2 days after operation. The thrombocytes had not been examined the leucocyte count on the day of death was 8,800. Penicillin and streptomycin had been administered as prophylactic antibiotic treatment, throughout the time f hospitalization

At autopsy the oesophageal anastomosis was found to hav partially opened and there was pus in the adjacent part f the mediastinum. The pleura on the right side had fibrinous covering, the air content was reduced in both lungs and pus oozed from the lung tissue on compression. There also was pus in the bronchi. Histological examination showed in both lungs pneumonic changes and a number of foci of haemorrhagic necrosis and in the small arteries partially obstructing arteritis. At the margins of the necrotic areas there were bacteria but only slight inflammatory cell reaction. Lung sample cultures yielded *Pseudomonas* and an unidentified gram negativ rod bacillus

Neonates with Oesophageal Atresia. Among the 26 *Pseudomonas*-colonized newborn infants the largest uniform group was comprised of the 13 patients with tresia f the oesophagus and one patient with tracheo-oesophageal fistula (Table 8) Nearly two-thirds f the 24 patients treated in the unit for oesophageal tresia during the period f this study were *Pseudomonas*-colonized.

Mort lity in the group of 24 neonates with oesophageal tresia during the period was 15 patients, or ove half of these patients (Table 12) Nine f those who died w re *Pseudomonas*-colonized. At a topsy pneumonia was confirmed in 7 of the latter whereas it was present in only one f the 4 non-colonized infants with oesophag eal tres who died.

In Table 12 the patients with oesophageal tresia are distributed into groups that ha e sign ficance from the point f prognosis (58, 171) The correl tions between these groups and *Pseudomonas* colonization, mortality and autopsy finding f pneumonia are presented.

Two f the newborn patients who on admission were in good general cond tion graded as A died 10 and 4 d ys fter operation in both cases pseudomonal pneumonia was diagnosed during

TABLE 12 *Condition on admission f neonates with oesophageal tresia and relationship to P eu dom colonization mortality and autopsy finding of pneumonia.*

	Pseudomonas-colonized			Non-colonized			Total		
	No of cases	No. of deaths	Pneumonia	No. of cases	No. of deaths	Pneumonia	No. f cases	No. of deaths	Pneumonia
Group A Birthweight over 2.5 kg good condition	4	2	2	5	0	0	9	2	2
Group B Birthweight 1.8–2.5 kg, good condition, or higher birthweight but child had also other anomalies or pneumonia	7	4	3	3	2	1	10	6	4
Group C Birthweight under 1.8 kg or higher but child had severe pneumonia or grav anomaly	3	3	2	2	2	0	5	5	
Total number of patients ith oesophageal atresia	14	9	7	10	4	1	24	15	8

life (Table 11 cases 5 and 13) The immediate cause of death of these two patients was rupture of the anastomosis.

In group B 6 newborn infants died, 4 of whom were *Pseudomonas*-colonized (Table 11 cases 1 7 10 and 11) Pseudomonal pneumonia had been diagnosed already during life in 2 cases and it was diagnosed at autopsy in a further case In 2 of these cases the immediate cause of death was rupture of the anastomosis.

All the infants in group C died Three were *Pseudomonas*-colonized and 2 of these had pneumonia which was observed during life in one case (Table 11 No 12) but not before autopsy in the other case (No 8)

Among the non-colonized 10 patients operated on for oesophageal atresia the anastomosis was found to be ruptured in one case only This patient had no signs of infection.

All the *Pseudomonas*-colonized infants in group A who recovered had been free from symptoms, while in group B one infant had had pneumonia and one conjunctivitis.

Various bacterial infections in the newborn One or more bacterial infections were found in 16 (14 %) of the 104 newborn infants under treatment in the unit during the period studied (Table 13) The largest number of infections were caused by gram negative bacilli i e six times as many as by *Staphylococci* Over a third of the bacillary infections were due to *Pseudomonas*, the following in frequency being those due to bacilli of the *Klebsiella* group and to *E. coli* Infections caused by various other gram negative bacilli as those of the *Proteus* and *Alcalescens Dispar* groups, *Alkaligenes faecalis* and others, formed a group of nearly the same size as that due to *Pseudomonas* alone

Among the newborn infants, carriers of the three most important pathogenic organisms, *Pseudomonas* *Klebsiella* and *Staphylococcus*, were about equal in number (Table 13) Nevertheless, the infections that developed during their stay in hospital were six times as often caused by *Pseudomonas* and *Klebsiella* as by *Staphylococcus* A finding of *Pseudomonas* at autopsy was remarkably more often associated with histological signs of infection than a finding of other bacteria (Table 13) The differences were statistically almost significant.

Antibiotic and gamma globulin treatment of the newborn During the period studied, anti-

TABLE 13 *Species of bacteria isolated from the neonate patients number of infections caused by them time of diagnosis of infection, and relationship to autopsy findings of infection*

Bacterium	Colonized neonates	Infections due to the bacterium	Symptoms on admission	Symptoms seen later: No of cases	Symptoms seen later: % of all neonates	No of deaths among colonized neonates	Autopsy findings of positive culture from lung and histological infection
Pseudomonas	26	1	3	14	14	13	11 **
Klebsiella	28	1[illegible]		10	10	10	2*
Escherichia coli	30	10	9	1	1		1
Other gram neg bacilli	39	16	7	9	[illegible]	[illegible]	2**
Staphylococcus aureus	25	9	5	4	4	2	2
Streptococcus haemolyticus	14	9	1	2	2	1	0
Other bacteria cultures neg	14	0	0	0	0	3	0

*) Both *Pseudomonas* and *Klebsiella* grew in the culture in one case

**) Both *Pseudomonas* and *Proteus vulgaris* grew in the culture in one case

biotics were used very extensively for prophylaxis. The commonly used combination was penicillin and streptomycin, with additionally chloramphenicol or some drug of the tetracycline group. During the first 3 months of the period, three or more antibiotics were administered to over a third of the infants admitted as newborn, and in the following 9 months to only a fifth of the neonates (Table 14). About half of the 104 hospitalized newborn received two antibiotics and only less than fourth had no antibiotic therapy. With one exception, all the *Pseudomonas*-colonized infants had received two or more antibiotics during at least 3 days before colonization was diagnosed. Statistically analysed there were almost significantly more Pseudomonas-colonized newborn infants in the group given antibiotics than in the group not administered these drugs.

During the first 3 months of the studied period 4 patients received polymyxin for the treatment of *Pseudomonas* infection. Colistin was given to 8 neonates, i.e. in 2 cases for treatment after finding of *Pseudomonas* colonization and in 6 cases for prophylaxis. One of the latter became colonized. All the patients who were given colistin were with one exception, under treatment during the last 2 months of the period studied.

Gamma-globulin was administered during the first 3 months to 4 neonate patients for treatment of diagnosed *Pseudomonas* infection. In the following 9 months 7 infants received gamma-globulin in 6 cases it was administered for prophylaxis and one of these infants became colonized.

B. Urological Patients

At some stage, *Pseudomonas* bacilli were isolated from the urine of 8 of the 22 urological patients treated in the paediatric surgical unit (Table 8). In 4 of these cases there was a positive finding in the urine on admission. 4 infants became colonized during hospitalization in the unit. Those found to be colonized on admission had been treated in the same unit 1—3 months earlier, and at that time *Pseudomonas* had appeared into the urine. In also these cases the contamination was possibly acquired in the unit. There were no cases of death among either *Pseudomonas*-colonized or non-colonized urological patients.

All the children found to have become colonized while in the unit had undergone an operation of the urinary tract 4—14 days before the finding of *Pseudomonas* in the urine and postoperatively they had had an indwelling catheter or other urinary tract drain during 3—10 days.

Pseudomonas was the only organism found in the urine of 4 patients, all of whom had definite pyuria and localized suppurating processes at the site of insertion of the drain. Body temperature was over 38 °C in one case only. The bacteriuria and pyuria persisted in these cases during the remaining 10—24 days of their stay in the hospital.

TABLE 14. Treatment of the neonate patients with antibiotics and relationship to *Pseudomonas* colonization during the first 3 months and the following 9 months of the present study

Number of antibiotics administered	Oct. 1 — Dec. 31 1962 No. of cases	Oct. 1 — Dec. 31 1962 Pseudomonas-colonized	Jan. 1 — Sept. 30, 1963 No. of cases	Jan. 1 — Sept. 30, 1963 Pseudomonas-colonized	Total No. of cases	Total Pseudomonas-colonized
3 or more antibiotics	13	8	14	4	27	12
2 antibiotics	16	6	58	7	64	13
1 antibiotic	0	0	1	0	1	0
No antibiotic	4	0	18	1	22	1
Total number of neonate patients	33	14	71	12	104	26

*) Colistin given as the other antibiotic to 6 infants.

life (Table 11 cases 5 and 13) Th immediate cause of death of these two patients was rupture of the anastomosis.

In group B 6 newborn infants died, 4 of whom were *Pseudomonas*-colonized (Table 11 cases 1 7 10 and 11) Pseudomonal pneumonia had been diagnosed already during life in 2 cases and it was diagnosed at autopsy in a further case In 2 of these cases the immediate cause of death was rupture of the anastomosis.

All the infants in group C died Three were *Pseudomonas*-colonized and 2 of these had pneumonia, which was observed during life in one case (Table 11 No 12) but not before autopsy in the other case (No. 8)

Among the non-colonized 10 patients operated on for oesophageal atresia the anastomosis was found to be ruptured in one case only This patient had no signs of infection.

All the *Pseudomonas*-colonized infants in group A who recovered had been free from symptoms, while in group B one infant had had pneumonia and one conjunctivitis.

Various bacterial infections in the newborn One or more bacterial infections were found in 46 (44 %) of the 104 newborn infants under treatment in the unit during the period studied (Table 13) The largest number of infections were caused by gram negative bacilli i.e., six times as many as by *Staphylococci*. Over a third of the bacillary infections were due to *Pseudomonas*, the following in frequency being those due to bacilli of the *Klebsiella* group and to *E. coli* Infections caused by various other gram negative bacilli as those of the *Proteus* and *Alcalescens Dispar* groups, *Alkaligenes faecalis* and others, formed a group of nearly the same size as that due to *Pseudomonas* alone

Among the newborn infants, carriers of the three most important pathogenic organisms, *Pseudomonas Klebsiella* and *Staphylococcus* were about equal in number (Table 13) Never theless, the infections that developed during their stay in hospital were six times as often caused by *Pseudomonas* and *Klebsiella* as by *Staphylococcus*. A finding of *Pseudomonas* at autopsy was remarkably more often associated with histological signs of infection than a finding of other bacteria (Table 13) The differences were statistically almost significant.

Antibiotic and gamma-globulin treatment of the newborn During the period studied, anti

TABLE 13 *Species of bacteria isolated from the neonate patients number of infections caused by them time of diagnosis of infection, and relationship to autopsy findings of infection*

Bacterium	Colonized neonates	Infection due to the bacterium	Symptoms on admission	Symptoms seen later: No. of cases	Symptoms seen later: % of all neonates	No of death among colonized neonates	Autopsy findings of positive culture from lung and histological infection
Pseudomonas	26	17	3	14	14	13	11 **
Klebsiella	28	12	2	10	10	10	2*
Escherichia coli	30	10	9	1	1	7	1
Other gram-negat bacilli	39	16	7	9	9	9	2*
Staphylococcus aureus	25	9	5	1	4	2	2
Streptococcus haemolyticus	14	9	1	2	2	1	0
Other bacteria cultures negati	14	0	0	0	0	3	0

) Both *Pseudomonas* and *Klebsiella* grow in th c lt i case

examination of the lungs showed extensive intra-alveolar and intrabronchial haemorrhages and atelectatic areas, many haemorrhagic necrotic foci, and in the small arteries partially occluding vasculitis. Inflammatory cell reaction was slight around the necrosed areas. No bacteria were seen. Growth of Pseudomonas was obtained in cultures of samples from the lungs.

The heart had a high ventricular septal defect and a truncus arteriosus communis.

Case B

A girl born on February 27, 1963, birthweight 2,690 g, had been hospitalized in this unit for the first time from February 27 to April 30, 1963 because of duodenal atresia and hydrocephalus. Retrocolic duodeno-jejunostomy was done when she was one day old. Postoperative recovery was good, but when the child was 3 weeks old myelomal... ventriculo-peritoneostomy was performed because of the rapidly progressing hydrocephalus. During her stay in the surgical unit a nose sample showed slight growth of *Pseudomonas* when she was 3 weeks old, but later samples were negative. Antibiotic prophylaxis was penicillin and streptomycin. When 1 1/2 months of age she was transferred to another hospital for observation.

She was re-admitted to the unit under study at the age of 7 months because of the progressive growth of the head. On admission the circumference of the head was 59 cm and her general condition was poor. The cerebrospinal fluid showed no inflammatory changes. *Pseudomonas* did not grow from nose and throat samples. On the day after re-admission a Spitz-Holter ventriculo-jugulostomy was done. On the fifth post-operative day her temperature rose to 39.5 C and she was vomiting; the cerebrospinal fluid contained 260 leucocytes per mm³ and large numbers of gram-negative bacilli, and culture yielded *Pseudomonas*. During her present stay in the unit she received no antibiotic prophylaxis; penicillin treatment was instituted after the meningitis had been diagnosed. The child's condition became progressively poorer, the febrile temperature fell, haemoglobin dropped to 6 g/100 ml and she died 17 days after operation.

Autopsy showed enormous cerebral ventricles. There was pus on the inner surface of the ventricles and on microscopic examination a thick layer of pus cells was seen on the meninges. Both lungs exhibited massive purulent pneumonia and circumscribed haemorrhagic necrotic foci, in the ... margin of which there was marked destruction of the walls of the small and medium-sized arteries by vasculitis. The right lung had a large haemorrhagic necrotic area about 5 mm in diameter and the adjacent medium-sized pulmonary artery showed necrotic vasculitis and obstructing thrombi. Adjacent to the necrotic area last mentioned there were histologically demonstrable bacteria. Foci of infection were also seen in the ..., heart and kidneys. Growth of *Pseudomonas* and *E. coli* was obtained in cultures of samples from the lungs.

Klebsiella was a finding concomitant with *Pseudomonas* in the urine of 4 patients. In these cases the *Klebsiella* probably had more significance, since *Pseudomonas* occurred only from time to time in the urine samples of these patients.

Bacteriuria developed in 10 of the 22 urological patients during hospitalization. Bacterial cultures from urine yielded *Pseudomonas* alone in one case only, *Pseudomonas* and *Klebsiella* in 3 cases, *Klebsiella* in 5 cases, and *E. coli* likewise in 5 cases.

C. Other Patients

Apart from the patients who were admitted to the paediatric surgical unit as newborn or as urological cases, a total of 387 children under 2 years were treated in the unit during the 12-month period studied (Table 5). Nineteen (5 %) of the latter were found to be *Pseudomonas* colonized. The finding was made on admission in 12 cases, or in 3 % of the patients. Seven children, or about 2 % of this group, became colonized later.

The greater part of the *Pseudomonas*-colonized children in this group were symptomless carriers of the organism in the nose and throat, totalling 12. Nine of these were *Pseudomonas*-colonized when admitted.

Symptoms of infection caused by *Pseudomonas* were seen in 7 children (1.8 % of the group). A urinary tract infection due to this organism developed in 2 children who had an indwelling catheter, a patient operated on for hydrocephalus had pseudomonal meningitis, and in one patient there developed a mixed infection with *Pseudomonas* and *Staphylococcus aureus* in the tracheal cannula wound. Already on admission 2 children had conjunctivitis and otitis and one patient had pneumonia, all caused by *Pseudomonas*.

In this group of 387 children there were 21 deaths. Four of those who died were *Pseudomonas*-colonized. In one case culture from the lung made at autopsy was positive for *Pseudomonas* but there were no signs of an infection. Another patient had had a mixed wound infection during life but at autopsy the lung culture and microscopic examination were negative for *Pseudomonas* and infection. Two children had during life had clearly a *Pseudomonas* infection, which was meningitis and septicaemia in one case and pneumonia in the other. In both cases the histological examination at autopsy revealed changes in the lungs typical of *Pseudomonas* infection. These patients are presented below.

Case 1

This patient was a girl born on July 13, 1965. Birthweight was 3 770 g and the Apgar score 9. Immediately after delivery a heart murmur was audible but the child progressed quite well during the first 4 weeks. At this time there was onset of respiratory difficulties and cyanosis, and when 6 weeks of age she was sent by the local hospital to the Children's Hospital of the Helsinki University Central Hospital.

The child was first admitted to the paediatric unit. Examination on admission showed a poor general condition, cyanosis, profuse mucus in the airways, systolic and diastolic heart murmur and enlargement of the liver to 5 cm below the costal arch. Body weight was 4,250 g. There was fever up to 38.5 C. Radiological findings were an enlarged heart and diffuse pneumonia in the right lower lobe. Samples were not taken for bacterial culture. Haemoglobin was 14.6 g/100 ml, leucocyte count 28,000 and thrombocyte count normal. Penicillin, erythromycin and ampicillin treatment and digitalization were instituted. Two days later she was transferred to the paediatric surgical unit because of the respiratory difficulty and was placed in a respirator. Nose and throat samples were taken on admission to the unit and yielded pure cultures of *Pseudomonas*. At this stage the child's temperature was normal, discharge of mucus continued to be very profuse and she could not manage without the respirator. Haemoglobin fell to 10.8 g/100 ml. The child died 4 days after admission to the surgical unit.

Autopsy revealed blood in the trachea and numerous haemorrhages beneath the pleura and on the cut surface of the lungs. Histological

The later cases of colonization during hospitalization occurred after *Pseudomonas*-colonized children with manifest infection had arrived in the ward. These may have been entirely separate epidemics.

Type of patients. It has been demonstrated that a hospital epidemic due to *Pseudomonas* arises readily when the type of patients susceptible to infections come into contact with heavy disseminators of the infective organism (99, 167). All the patients in the unit under study were susceptible because of their age, a marked proportion of them had received large amounts of antibiotics for prophylaxis, and throughout the studied period part of the patients were premature or full-term neonates with various congenital anomalies who had undergone major operations, i.e. patients of the type found to be particularly susceptible to infection with *Pseudomonas* (15, 23, 56, 72, 79, 160, 175, 180).

As heavy disseminators of *Pseudomonas* bacilli can be regarded especially the infected urological patients (106, 150, 164) and the patients with various forms of superficial purulent *Pseudomonas* infections or with pneumonia. A relatively large number of such patients were being treated in the unit especially at the beginning and end of the studied period.

Hygiene in the unit. During the first few months of the period studied no systematic efforts were made to prevent the spreading of *Pseudomonas* bacilli. The *Pseudomonas*-colonized children were treated with the non-colonized ones in the ward and the operating theatre with no isolation measures of any kind being taken. Hexachlorophene and benzalkonium chloride substances that are poorly effective against *Pseudomonas* were used for the disinfection of the hands, equipment and environment.

After the first 3 months of the period the children found to be *Pseudomonas*-colonized were systematically isolated, and greater emphasis was placed on hand hygiene and on the cleansing and sterilization of equipment and utensils. However, no change was made in the disinfectants used.

Relative importance of the different factors. It is seen from the foregoing that during the first 3 months of this study there existed all the preconditions for continuation of the earlier epidemic. The definite decrease in the number of cases thereafter may possibly be ascribed to a number of causes. Among these reasons were most probably the removal from the unit of at least the transmitters of massive contagion and the destruction *of foci of infection* in the equipment through more efficient control and cleansing.

Twice later *Pseudomonas* was again found to have spread among the patients in the unit probably following the admission of heavily *Pseudomonas*-infected patients. These patients were in poor condition on arrival and they needed much attention and handling; furthermore the presence of the *Pseudomonas* infection was not known in all cases on admission and this facilitated spreading of the organism. Very probably the ceasing of the epidemic at both times (the last epidemic did not continue beyond the period of this study) was to a marked extent brought about by improved hygiene in the unit and possibly also by alterations in antibiotic prophylaxis.

Possible Routes of Transmission of *Pseudomonas*

Transmission by hands. A number of patients who may be considered to have caused heavy contamination of the hands of the nursing staff were hospitalized in the unit during the investigated period, particularly at the various times when spreading of *Pseudomonas* was noted. Such probable contaminators were urological patients with *Pseudomonas* infection, patients with suppurating wounds, and patients with severe pneumonia and a copious *Pseudomonas* flora in the discharge from the throat and trachea. Many of these infants were in poor condition and required much handling, and the numerous emergency situations that occurred allowed no time for precautionary measures.

Discussion

Nature of Occurrence of *Pseudomonas*

Pseudomonas bacilli were isolated from a rather large proportion, 10 %, of patients treated in the paediatric surgical unit during the 12 month period of study Since a systematic search was not made for faecal and skin carriers, the number of carriers was presumably still greater (22, 18 116) According to the literature, the frequency incidence of *Pseudomonas* colonization among the non hospital population of the same age is in general lower and therefore the incidence obtained in this study points to contamination acquired in the hospital environment.

Half of the *Pseudomonas* carriers found were colonized already at the time of admission to the unit earlier hospital contacts should presumably be regarded as the sources of the bacillus in these cases. Whereas the children found to be colonized on admission were fairly evenly distributed over the period studied, the figures for those colonized while in the unit were highest in October December 1962, March April 1963 and August-September 1963. Into these periods were also centred most of the diagnosed *Pseudomonas* infections, *Pseudomonas* positive cultures from lung samples at autopsy and the heaviest environmental contamination in the unit.

The patients who died particularly in this unit gave *Pseudomonas* positive cultures from lung samples at autopsy in a very high incidence of cases. This incidence was of the same order of magnitude as that reported earlier in the literature (132) and differed statistically significantly from the incidence among infants dying during the same period in the praematures ward and the infection ward for children under 2 years o age.

Since facilities for the typing of *Pseudomonas* strains were not yet available at the time the present study was made, definite conclusions can not be drawn concerning the source and mode of transmission of the strains found in the patients and in the unit environment. However in the light of the results presented it appears probable that conditions in the paediatric surgical ward and operation unit were favourable for the spreading of *Pseudomonas* bacilli and infections, especially during the first three and last two months of the period studied.

Factors Promoting Outbreak of the Epidemics

Source of Pseudomonas The observation has been reported in the literature that one and the same *Pseudomonas* type may give rise to infections in the same hospital unit in the course of many weeks and even of months (167) In the paediatric surgical unit studied in the present investigation there had occurred numerous cases of *Pseudomonas* infection during the months preceding the commencement of the investigation in October 1962, and some cases had been observed already in 1961 (132) A part of the *Pseudomonas*-colonized patients under treatment in the unit in the early part of th studied period had had the infection already before the study was begun, and it is therefore very probable that the numerous cases of *Pseudomonas* infection during the first months of study were a continuat on of an earlier p demic.

The later cases of colonization during hospitalization occurred after *Pseudomonas*-colonized children with manifest infection had arrived in the unit. These m y h   been entirely separate epidemics.

Type of patients. It has been demonstrated that   hospital epidemic due to *Pseudomonas* arises readily when the type of patients susceptible to infections come into co tact with heavy *disseminators* f the infecti e organism (99, 167). All the patients in the unit under study were susceptible because of their age,   marked proportion f them had received large amounts of antibiotics for prophylaxis, and throughout the studied period   part f the patients were praemature or full-term neonates ith   arious congenital anomalies who had undergone major operations, i.e. patients of the type found to be particularly susceptible to infection with *Pseudomonas* (15, 23 56, 72, 79 160, 175 180).

As heavy disseminators of *Pseudomonas* bacilli can be regarded especially the infected urological patients (106, 150, 164) and the patients ith   arious forms f superficial purulent *Pseudomonas* infections or w th pneumonia. A relatively large number of such patients were being treated in the unit especially at the beginning and end f the studied period.

Hygiene in the unit. During the first few months of the period studied no systematic efforts were made to prevent the spreading f *Pseudomonas* bacilli. The *Pseudomonas*-colonized children   ere treated with the non-colonized ones in the ward and the operating theatre with no isolation measures of any kind being taken. H xa chlorophene and benzalkonium chlorid   substances that are poorly effecti   against *Pseudomonas*, were used for the disinfection f the hands, equipment and environment.

After the first 3 months f the period the children found to be *Pseudomonas*-colonized were systematically isolated, and greater emphasis as placed on hand hygiene and on the cleansing and sterilization of equipment and utensils. However no change was made in the disinfect ants used.

Relative importance f the different factors. It is seen from the foregoing that during the first 3 months f this study there existed all the pre-cond tions fo   continuation f the earlier epidemic. The definite decrease in the number of cases thereafter may possibly be ascribed to a number f causes. Among these reasons were most probably the removal from the unit of at least the transmitters f massi   contagion and the destruction f foci f infection in the equipment through more efficient control and cleansing.

Twice l ter *Pseudomonas* was again found to hav spread among the patients in the unit probably following the admission of heavily *Pseudomonas*-infected patients. These patients were in poor condition on arrival and they needed much ttention and handling furthermore, the presence of the *Pseudomonas* infection was not known in all cases on admission and this facil itated spreading of the organism. Very probably the ceasing of the epidemic t both times (the last epidemic did not continue beyond the period f this study) was to a m rked extent brought about by improved hygiene in the unit and possibly also by alterations in antibiotic prophylaxis.

Possible Routes of Transmission of *Pseudomonas*

Transmission by hands. A number of patients who may be considered to h   caused heavy contamination f the hands of the nursing staff were hospitalized in the unit during the investigated period, particularly at the various times when sp eading f *Pseudomonas* was noted. Such probable contaminators were urological patients with   *Pseudomonas* infection, patients with suppurating wounds, and patients with severe pneumonia and   copious *Pseudomonas* flora in the discharge from the throat and trachea. Many f these infants were in a poor condition and required much handling, and the numerous emergency situations that occurred allowed no time for precautionary measures.

Although no actual evidence can be presented for the transmission of part of the infection by the hands of the staff the conclusion that the hands were contaminated can be drawn from the finding of contamination in the stationary washbasins, especially in rooms where there were *Pseudomonas*-colonized patients. Earlier studies have shown that after massive contamination with *Pseudomonas* it is difficult to fully free the hands of the organism even by meticulous washing and disinfectants (100) Furthermore hexachlorophene, which was used in cleansing of the hands at the time of the present study has a weak action against *Pseudomonas* On these grounds it appears very probable that the handling of a massively contaminated patient led to transmission of the infective agent either to another patient or to hospital equipment.

Transmission by hospital equipment In this study *Pseudomonas* was isolated from several items of ward and operation unit equipment, instruments and furniture of kinds that very probably can transmit an infective agent.

Pseudomonas was obtained from the rubber tube and tube connector of an anaesthesia machine during the second month of this study At that time the machines were still being used for the anaesthetization of a number of patients successively in the course of the day and were cleaned only after operations were finished for the day Since at this time the *Pseudomonas* colonized patients were treated in the operation room along with the other patients, it seems quite evident that the organism may have entered the respiratory tract of the following patients by this means. Transmission of infection by way of anaesthesia machines has been described in the literature possibly an anaesthetized patient is more susceptible to contract infection of the lungs (71 152, 179 181)

Evidence speaking for transmission by the anaesthesia equipment in the present study are the large number of lung infections and of *Pseudomonas* positive cultures from lung samples during the first months of the study period. Furthermore the organism was not found in other equipment that would have been able to convey it into the respiratory tract, as nebulizers, oxygen equipment and respirators.

On the other hand, the organism was found in the kitchen sink and a kitchen brush and in bottles for continuous drip-feeding of newborn that were assumed to be sterile The unit had no facilities for the sterilization of food dishes by boiling the dishes of isolated patients were immersed for a time in a solution of benzalkonium chloride and then washed in the usual manner The food proteins presumably reduced further the low potency of this solution and the dishes may have still been contaminated after the cleaning process.

The positive bacterial cultures obtained from the stationary washbasins are possibly of little significance in the spreading of the infection and may be considered only a sign of contamination of the hands in the ward and operation unit. The bacillus was not found in samples taken from the mouth of the water tap which would have suggested contamination of the water but only from the mouth of the washbasin drain.

Infection with *Pseudomonas* has been observed to spread from patient to patient in connection with bathing (165) The organism was found in bathtub drains at only about the middle and end of the studied period and even in those cases in the bathtubs of rooms where *Pseudomonas* colonized patients were isolated. Bathtubs may possibly have been one of the routes of transmission in the early period when the colonized patients were housed among the non-colonized even if the cultures of samples from the bathtubs were negative for *Pseudomonas*

Most of the newborn were postoperatively placed in incubators Only one finding of *Pseudomonas* was made in this type of equipment and this particular incubator was thoroughly cleaned until repeated bacterial cultures were negative Transmision of the infective agent by this route therefore seems unlikely

In the sluice room, infection may naturally have spread from heavily contaminated brushes to the utensils being cleaned and to the hands of the personnel and thus back into the ward to other patients.

The possibility cannot be excluded that infection may have been transmitted also by means of items of equipment which were not examined for Pseudomonas or which at the time of examination were uncontaminated.

Since facilities were not available for typing of the Pseudomonas strains found in the equipment used in the unit it is not possible to conclude whether or not these strains were identical with those that caused symptoms of infection in the patients. In any case it can be said that the contamination of hospital equipment constituted a marked infection hazard to the patients.

Transmission by air and dust. Especially in the case of epidemic respiratory tract infections caused by Pseudomonas, transmission by air has been considered a decisively important route in the spreading of the infection. Since during the period studied Pseudomonas was not found either on the settling plates or in floor dust, transmission by this route appears to have been of minor significance.

Transmission by the hospital staff. Since no nasal or throat carriers of Pseudomonas were found in either the ward or the operation unit staff transmission in this manner seems unlikely. However the staff was not examined for faecal carriers and there might have been members of the personnel who were carriers of an epidemic Pseudomonas strain. Earlier studies have shown, however, that faecal carriers of Pseudomonas in hospital staffs are generally very few in number and of minor significance in the transmission of the infectious agent (18, 22, 99).

Occurrence and Significance of *Pseudomonas* Infections

Although all the patients treated in the paediatric surgical unit for children under 2 years of age can be considered to be susceptible to Pseudomonas infection (81), the Pseudomonas-colonized patients and those who developed symptoms of the infection were mostly found among the neonatal and urological patients. In addition to the clearly demonstrated susceptibility of these groups to infections with gram-negative bacilli of all kinds, a number of other factors may also have contributed to the high incidences in these two groups of patients.

These were patients who were being most closely observed and from whom samples were frequently taken for bacterial culture. In the other groups there were conspicuously large numbers of patients in good condition whose stay in the hospital lasted only a few days and from whom samples for culture were taken once only. It is possible that the number of transient Pseudomonas-colonized children in this group actually was greater than that shown by the cultures. The true incidence of infections, on the other hand, was presumably not notably higher than that stated, since a relatively large proportion of these children were hospitalized in the unit a number of times during the period under study and no Pseudomonas infections were found in them.

Both the patients admitted as newborn and the urological patients required after operation a considerable amount of handling in connection with suction drainage, fluid therapy and feeding, and these manipulations provided an opportunity for the transmission of infection. Patients with oesophageal atresia in particular suffer from very copious mucus in their airway postoperatively (156) and need repeated bronchial toilettes and suction. During these procedures, Pseudomonas flora present in the throat may be conveyed to the lower respiratory passages, where favourable conditions exist for the spread of infection because of the frequently poor respiratory function of these patients. For the same reason, transmission by way of an anaesthesia machine can be assumed to result readily in pneumonia. Colonization of patients with oesophageal atresia may also be promoted by the high humidity conditions necessary in their care (69). Possibly the exceptionally great susceptibility to Pseudomonas infections which has frequently been observed in patients with oesophageal atresia (15, 23, 56) and which was evident also in the present series is based on these postoperative factors.

The absence during the studied period of *Pseudomonas* infections in the patients with burns, who are known to be susceptible to this organism, was probably due to the low grade of the burns. Infection with *Pseudomonas* has been found to occur most readily in cases of severe and extensive burns (99)

The *Pseudomonas* infections that occurred in the unit during this investigation were well in agreement with the cases described in the literature with respect to incubation time, symptoms, bacterial findings, duration of illness and prognosis. However in a patient series such as this it often was difficult to ascribe an infectious origin to the symptoms, since poor weight gain vomiting or diarrhoea could well have been associated with the basic disease in many cases. On the other hand occasional cases have been described in which these were the only symptoms of neonatal infection with *Pseudomonas* (22) The symptoms from the respiratory tract could also be readily attributed to the basic pathological condition for example atresia of the oesophagus. For these reasons a part of the *Pseudomonas* colonized newborn infants who actually had symptoms of the infection may have been included in the group of asymptomatic patients, and these cases thus had only the effect of possibly increasing the figure for the mean length of hospitalization of the group of colonized infants. Difficulties were encountered especially in interpreting abdominal distention and vomiting — an ileus type of condition that according to the literature is frequently present also in *Pseudomonas* infections (72 145) These symptoms were erroneously regarded as indications for explorative laparotomy on the suspicion of intestinal obstruction in two patients with pneumonia during the studied period

Histological changes in the lungs typical of *Pseudomonas* infection were found at autopsy in less than half of the newborn infants who died with definite clinical symptoms of this infection. One of the reasons may have been the difficulty of interpretation of diffuse pneumonia and diffuse haemorrhage in neonates and the fact that specimens for microscopical examination had not been taken in cases of peritonitis from the most severely infected organ, the intestine. Reports in the literature indicate, however that such changes do not always occur even in definite cases of *Pseudomonas* infection (23, 40).

The high mortality incidence in the diagnosed cases of *Pseudomonas* infection in the newborn series is also compatible with the data in the literature. *Pseudomonas* infection in itself has a high mortality and, in addition infection in general is known to have a poor prognosis in neonates who are in a poor condition and suffer from anomalies (1 2, 121)

The *Pseudomonas*-colonized newborn infants who died were not all in the poorest category of surgical prognosis, though they included a large number of neonates in the praematures weight range or with one or more congenital anomalies. In the group with oesophageal atresia, 5 children died who can be considered to have been quite good surgical risks (patients No. 1 5, 10, 11 15). In these cases the *Pseudomonas* infection should probably be regarded as at least a contributory cause of death. In 4 of these cases the immediate cause was rupture of the anastomosis, but the *Pseudomonas* infection may be said to have promoted the opening of the anastomosis.

Whether the reason for the high mortality especially during the early part of the period under study was a higher virulence of the epidemic strain of *Pseudomonas* prevalent at the time or possibly a more massive contamination is a question that will remain open The change made in the treatment may well have contributed to the more favourable prognosis in the later period The marked use of antibiotics possessing a weak action against *Pseudomonas* in the early period may even have promoted the infection (115 177) while the prophylactic administration of colistin and gamma globulin n the later period may have had a part in reducing the number of cases of *Pseudomonas* infection (132)

In the groups of paediatric surgical patients other than those admitted to the unit as newborn, the mortality among *Pseudomonas*-colonized children was fairly low and an infection caused by this organism can be r garded as the

immediate cause of death in two cases only. The prognosis for these two children was poor already because of the basic disease: one patient had a grave congenital heart defect and the other patient had already once earlier undergone an operation for hydrocephalus. The literature however, contains reports of severe *Pseudomonas* infections of septicaemia type in urological patients, especially after operation, with a high mortality in some series (55, 56). Even a low grade infection in our urological patients must be considered to have been a risk to life. Furthermore the bacteruria, in some cases of several weeks' duration, prolonged the length of hospitalization and possibly also impaired the surgical result (140).

Klebsiella infections, however, appeared to present a greater problem in the urological patients during the period studied than the *Pseudomonas*. Among neonates, on the other hand, *Pseudomonas* was clearly of greater consequence than *Klebsiella* as the causative agent of hospital infection. In the course of the present study clear indications were obtained of the marked importance of also other gram-negative rod bacteria as cause of infections, as compared with the formerly so common *Staphylococcus*.

Pseudomonas is known to produce infections with a rapidly fatal course (52) as well as disease conditions of a long duration (39, 52, 55). Presumably for this reason the length of hospitalization of the *Pseudomonas*-colonized children varied over such a wide range that a statistically significant difference from the non-colonized infants could not be established. In individual cases, however, the infection can be said to have prolonged the duration of treatment of newborn infants in the surgical unit. On the other hand, it is difficult to evaluate the effect of *Pseudomonas* colonization in the older children, since most of them were fully symptomfree carriers of the organism and the remainder had rather mild local symptoms of short duration, except for the fatal cases referred to above. Naturally also these infections constituted a certain hazard to the patients.

The absence during the studied period of *Pseudomonas* infections in the patients with burns, who are known to be susceptible to this organism, was probably due to the low grade of the burns. Infection with *Pseudomonas* has been found to occur most readily in cases of severe and extensive burns (99).

The *Pseudomonas* infections that occurred in the unit during this investigation were well in agreement with the cases described in the literature with respect to incubation time, symptoms, bacterial findings, duration of illness and prognosis. However, in a patient series such as this it often was difficult to ascribe an infectious origin to the symptoms, since poor weight gain, vomiting or diarrhoea could well have been associated with the basic disease in many cases. On the other hand, occasional cases have been described in which these were the only symptoms of neonatal infection with *Pseudomonas* (22). The symptoms from the respiratory tract could also be readily attributed to the basic pathological condition, for example atresia of the oesophagus. For these reasons a part of the *Pseudomonas*-colonized newborn infants who actually had symptoms of the infection may have been included in the group of asymptomatic patients, and these cases thus had only the effect of possibly increasing the figure for the mean length of hospitalization of the group of colonized infants. Difficulties were encountered especially in interpreting abdominal distention and vomiting — an ileus type of condition that according to the literature is frequently present also in *Pseudomonas* infections (72, 145). These symptoms were erroneously regarded as indications for explorative laparotomy on the suspicion of intestinal obstruction in two patients with pneumonia during the studied period.

Histological changes in the lungs typical of *Pseudomonas* infection were found at autopsy in less than half of the newborn infants who died with definite clinical symptoms of this infection. One of the reasons may have been the difficulty of interpretation of diffuse pneumonia and diffuse haemorrhage in neonates and the fact that specimens for microscopical examination had not been taken in cases of peritonitis from the most severely infected organ, the intestine. Reports in the literature indicate, however, that such changes do not always occur even in definite cases of *Pseudomonas* infection (93, 10).

The high mortality incidence in the diagnosed cases of *Pseudomonas* infection in the newborn series is also compatible with the data in the literature. *Pseudomonas* infection in itself has a high mortality and in addition infection in general is known to have a poor prognosis in neonates who are in a poor condition and suffer from anomalies (1, 2, 101).

The *Pseudomonas*-colonized newborn infants who died were not all in the poorest category of surgical prognosis, though they included a large number of neonates in the prematures weight range or with one or more congenital anomalies. In the group with oesophageal atresia, 5 children died who can be considered to have been quite good surgical risks (patients No. 1, 5, 10, 11, 15). In these cases the *Pseudomonas* infection should probably be regarded as at least a contributory cause of death. In 4 of these cases the immediate cause was rupture of the anastomosis, but the *Pseudomonas* infection may be said to have promoted the opening of the anastomosis.

Whether the reason for the high mortality especially during the early part of the period under study was a higher virulence of the epidemic strain of *Pseudomonas* prevalent at the time or possibly a more massive contamination is a question that will remain open. The change made in the treatment may well have contributed to the more favourable prognosis in the later period. The marked use of antibiotics possessing a weak action against *Pseudomonas* in the early period may even have promoted the infection (145, 177), while the prophylactic administration of colistin and gamma globulin in the later period may have had a part in reducing the number of cases of *Pseudomonas* infection (132).

In the groups of paediatric surgical patients other than those admitted to the unit as newborn, the mortality among *Pseudomonas*-colonized children was fairly low and an infection caused by this organism can be regarded as the

References

1. Ahvenainen, E. K. A study of causes of neonatal death. J Pediat, *55*:691, 1959.
2. Ahvenainen, E. K. The role of infection in the mortality of premature infants. Ann Paediat Fenn, *10*:243, 1964.
3. Alanen, R. & Pyyhtinen, P. *Johdatusta tilastolliseen tutkimukseen.* (Introduction to statistical investigation.) University of Helsinki, Helsinki 1964, 4th ed.
4. Alexander, J. W., Brown, W., Walker, H., Mason, A. D. Jr. & Moncrief, J. A. *Studies on the isolation of an infection-protective antigen from Pseudomonas aeruginosa.* Surg Gynec Obstet, *123*:965, 1966.
5. Allansmith, M., McClellan, B. H., Butterworth, M. & Maloney, J. R. The development of immunoglobulin levels in man. J Pediat 72:276, 1968.
6. Alms, T. H. & Bass, J. A. Immunization against *Pseudomonas aeruginosa.* I. Induction of protection by an alcohol-precipitated fraction from the slime layer. J Infect Dis, *117*:249, 1967.
7. Altemeier, W. A. Bodily response to infectious agents. JAMA, 202:1085, 1967.
8. Altemeier, W. A. & Smith, R. T. Immunologic aspects of resistance in early life. Pediat Clin N Amer *12*:663, 1965.
9. American Academy of Pediatrics Committee on fetus and newborn. Decontamination. [illegible] in neonatal units. Pediatrics, *38*:142, 1966.
10. Amiel, C., Fleurquin, U., Larroche, J. C. & Minkowski, A. A propos de 18 observations d'infections à *Pseudomonas* du nouveau-né. Considérations épidémiologiques. Arch Franç Pédiat, *23*:1113, 1966.
11. Anderson, K. *Pseudomonas pyocyanea* disseminated from air-cooling apparatus. Med J Aust, *1*:529, 1959.
12. Anderson, K. The contamination of hexachlorophene soap with *Pseudomonas pyocyanea.* Med J Aust, *49*:463, 1962.
13. Anderson, N. A., Sage, D. N. & Spaulding, E. H. Oral moniliasis in newborn infants. Amer J Dis Child 67:450, 1944.
14. Arseni, A. E. & Doxiadis, S. A. Faecal carriage of *Pseudomonas.* Lancet, *I*:837, 1967.
15. Asay, L. D. & Koch, R. *Pseudomonas* infections in infants and children. New Eng J Med, *262*:1062, 1960.
16. Aurelius, G. Bacterial growth in urine. Acta Path Microbiol Scand, *55*:201, 1962.
17. Ayliffe, G. A., Lowbury, E. J. L., Hamilton, J. G., Small, J. M., Asheshov, E. A. & Parker, M. T. Hospital infection with *Pseudomonas aeruginosa* in neurosurgery. Lancet, *II*:365, 1965.
18. Ayliffe, G. A., Barry, D. R., Lowbury, E. J. L., Roper-Hall, M. J. & Walker, W. M. Post-operative infection with *Pseudomonas aeruginosa* in an eye hospital. Lancet, *I*:1113, 1966.
19. Barber, M. Hospital infections yesterday and today. J Clin Path, *14*:2, 1961.
20. Barber, M. & Waterworth, P. M. Activity of Gentamicin against *Pseudomonas* and hospital staphylococci. Brit Med J *1*:203, 1966.
21. Barrie, D. Incubator-borne *Pseudomonas pyocyanea* infection in a newborn nursery. Arch Dis Child, *40*:555, 1965.
22. Bassett, D. C. J., Thompson, S.A.S. & Page, B. Neonatal infections with *Pseudomonas aeruginosa* associated with contaminated resuscitation equipment. Lancet, *I*:781, 1965.
23. Bernstein, J. & Wang, J. The pathology of neonatal pneumonia. Amer J Dis Child, *101*:350, 1961.
24. Blaker, F., Landbeck, G. & Fischer, K. Antikörper-Mangel infolge langfristiger cytostatischer Behandlung bei malignen Tumoren und akuten Leukosen im Kindesalter. Indikationen zur γ-Globulintherapie. Mschr Kinderheilk, *115*:93, 1967.
25. Bodey, G. P. Pulmonary complications of acute leucaemia. Cancer *19*:781, 1966.
26. Bøvre, K. Bakteriell [illegible]. Noen genetiske og molekylære prinsipper. Nord Med, 79:4, 1968.
27. Brayton, R. C. & Louria, D. B. Gentamicin in gram-negative urinary and pulmonary infections. Arch Intern Med (Chicago), *114*:205, 1964.

Summary

This investigation was undertaken with the object of clarifying the occurrence and significance of the *Pseudomonas* bacillus in the surgical unit of the Children's Hospital of the Helsinki University Central Hospital in the period from October 1 1962 to September 30 1963. During this period a total of 513 surgical paediatric patients, ranging in age from newborn to about 2 years, were treated in the unit.

Pseudomonas bacilli were isolated from 53 of these patients. In 25 cases the children arrived fairly evenly throughout the period studied. The 28 children who became colonized during stay in the unit were on the other hand, mainly concentrated into three periods October December 1962 March April 1963 and August September 1963

In bacteriological examinations of hospital equipment, *Pseudomonas* was isolated from, e g an anaesthesia machine the sink and a brush in the unit's kitchen glass bottles used in the drip-feeding of neonates, and an incubator The largest number of contaminated objects were found during the first months of the investigation

The incidences of *Pseudomonas*-colonized children were highest in the groups of neonate and urological patients Of the newborn 25 per cent were colonized and 16 per cent had symptoms of *Pseudomonas* infection The organism was isolated from the urine of one third of the urological patient The incidence of *Pseudomonas* colonization among the other paediatric surgical patients in the unit was only 5 per cent and the incidence of symptoms of *Pseudomonas* infection was 1 8 per cent.

The largest group of *Pseudomonas*-colonized neonates was comprised of patients with atresia of the oesophagus. Pneumonia was the most frequent symptom Infections due to *Pseudomonas* were the most common bacterial infections encountered among the newborn. During stay in hospital *Pseudomonas* infections developed in 14 per cent those due to *Klebsiella* group rods in 10 per cent and to *Staphylococcus* in 4 per cent of the infants admitted to the unit as newborn.

Seventeen of the *Pseudomonas*-colonized children died 13 of them had been admitted as newborn. At autopsy a *Pseudomonas* positive culture was obtained from lung samples in 13 cases, in which there also were histological signs of infection Histological changes specific for *Pseudomonas* infection were found in 5 cases only

The following conclusions were drawn from the results obtained in this study

1 A hospital infection type of spreading of *Pseudomonas* bacilli occurred in the ward and operation unit of the paediatric surgical unit of the Children's Hospital during the period of the present investigation.

2 A number of causes apparently were factors contributing to outbreak of the epidemic During the period studied there were in the unit numerous patients of types susceptible to *Pseudomonas* infection and many who were massive transmitters of infection The routine hygienic measures in the unit although well able to prevent spread of *Staphylococcus* were inadequate for *Pseudomonas*

3. Transmission of *Pseudomonas* is suspected to have occurred by the hands of the hospital staff and by means of contaminated hospital equipment

4 *Pseudomonas* infection prolonged the stay in hospital and impaired the prognosis of the paediatric surgical patients, especially of those who had entered the unit as newborn

61 Gould, J. C. *Pseudomonas pyocyanea* infections in hospital. In R. E. O. Williams & R. A. Shooter (eds) *Infection in hospitals*. Da is, Philadelphia 1963, pp. 119–130.

62 Gravroos, J. A. Pal a, T & Salobeimo, M.L. Bronchoscopic observations in pulmonary tuberculosis, ith special reference to cytologic and bacterial findings. Acta Tuberc Scand, 32:165, 1956

63 Haffner, F. D., Voter E. & Rubin, M. L. Penicillin and its effect in producing predominant gram-negativ bacillary flora in upper respiratory tract f children Pediatrics, 6:202, 1950.

64 Hillstrom, K. Desinf kitoaineiden kaytto sairaalassa (Use of disinfectants in hospital.) Suom Laak, 22:2310, 1967

65 Haselhuhn, D H Brason, F W & Borick, P M. In use study of buffered glutaraldehyde for cold sterilization of anesthesia equipment. Anesth Analg (Cleveland), 46:468, 1967

66 Hatt, I. J & Petiot, M. Affections à pyocyanique du nouveau-né et l'enfant 8 observations Pédiatrie, 18:975,1963

67 Hitchings, G. H & Elion, G. B. Chemical suppression of the immune response. Pharmacol Rev 15 :67 1963

68 Hobbs J. R. & Davis, J. A Serum γ-G-globulin levels and gestational age in praematurc babies. Lancet, I 757 1967

69 Hoffman, M A & Finberg, L Pseudomonas infections in infants associated w th high humidity environments J Pediat, 46:626, 1955

70 Hurst, V & Sutter V L Survival of *Pseudomonas aeruginosa* in the hospital environment. J Infect Dis, 116:151 1966

71 Isalo E Anestesiavalmeiston aiheuttaman infektion torjunta (The prevention of infection caused by anesthetic equipment) Duodecim, 83:76, 1967

72 Jacobs J The in estigation of an outbreak f *Pseudomonas aeruginosa* in podiatric units. Postgrad Med, 40 :90 1964

73 Jao, R L & Jackson, G G Gentamicin sulfate, new antibiotic against gram-negati bacilli Laboratory pharmacological and clinical evaluation JAMA, 189:817 1964

74 Jedličková, Z & R 6, M Zum Probleme der A tibiotikakombinationen bei *Pseudomonas aeruginosa* in ro Z Ges Inn Med, 22:215, 1967

75 Johnston R B J & Sell, S. H Septicemia in infants and hildren Pediatrics, 34:473, 1964

76 James, R J & Lowbury E J L Susceptibility of man to *Pseudomonas aeruginosa*. Preliminary communication Lancet, II:625, 1965.

77 Kalmár P & Ott, H. Pyocyaneus-Meningitis. Deutsch Med Wschr 87.:90, 1962.

78. Kalser M. H., Cohen, R., Arteaga, I Y wn, E., Mayoral, L., Hoffert, W R. & Frazier D: Normal iral and bacterial flora of the human small and large intestine New Eng J Med, 274 500, 1966.

79. Kangos, J J Septicemia in infancy The incidence of associ ted ongenital nomalies. Arch Pediat, 67:09, 1950.

80. Kauffmann, F *Enterobacteriaceae* Ejnar Munksgaard, Copenhagen 1954 2nd ed.

81 Kefalides, N A., Arana, J A., Bazan, A., Velarde N & Rosenthal, S. M. E aluation of antibiotic prophylaxis and gammaglobulin, plasma, albumin and saline-solution therapy in severe burns Ann Surg, 159 490, 1964.

82 Kenn J F Boesman, M. I & Michaels, R. H. Bacterial and iral coproantibodies in breastfed infants Pediatrics, 19 202, 1967

83. Keown, K K Gilman, R A. & Bailey C. P Ope heart surgery Anesthesia and surgical experiences JAMA, 165 781 1957

84 Kislak, J W Eickhoff T C. & Finland, M. Hospital-acquired infections and antibiotic usage in the Boston City Hospital New Eng J Med, 271:834 1964

85 Knights, H T & Harvey J Hand creams containing hexachlorophene and cross infections w th gram negati bacteria. New Zeal Med J 63:635, 1964

86. Kortekangas, A. E I estigations of the bacterial flora f the respiratory tract. Acta Otolaryng (Stockholm), suppl. 150, 1959

87 Kortekangas, A. E. Otitis media ac. Duodecim, 80 486, 1964

88 Kou alainen, K Gammaglobuliini terapeuttisena ja profylaktisena laakeaineena (Gammaglobulin as therapeutic and prophylactic drug). Duodecim, 82 479, 1966.

89 Kresky B. Control of gram-negativ bacilli in hospital nursery Amer J Dis Child, 107:363, 1964

90 Lányi, B Gregács, M. Ádám, M. M. Incidence of *Pseudomonas aeruginosa* serogroups in water and human faeces. Acta Microbiol Acad Sci Hung, 67 319 1966.

91 Laurenzi, G A., Potter, R. T & Kass, E. H. Bacteriologic flora of the lower respir tory tract. New Eng J Med, 265 1273, 1961

92 Laursen, H. Incidence of *Pseudomonas aeruginosa* and other gram-negati rods in newborn infants. Acta Obstet Gynec Scand, 41:254 1962.

28. Brumfitt W Percival, A & Leigh, D A. Clinical and laboratory studies with Carbenicillin. A new penicillin active against *Pseudomonas pyocyanea*. Lancet, *1* 1289 1967

29. Burns, M W & May J R. Bacterial precipitins in serum of patients with cystic fibrosis. Lancet, *1* 270, 1968.

30. Caselitz, F H. *Pseudomonas Aeromonas und ihre humanmedizinische Bedeutung* VEB Gustav Fischer Verlag Jena 1966.

31 Cason J S & Lowbury E J L. Prophylactic chemotherapy for burns. Lancet, *II* 501 1960.

32. Cason, J S. & Lowbury E. J L. Mortality and infection in extensively burned patients treated with silver nitrate compresses. Lancet, *1* 651 1968.

33. Cocchi P & Mariancili L. Phagocytosis and intracellular killing of *Pseudomonas aeruginosa* in premature infants. Helv Paediat Acta, 2. 110 1967

34 Cohen R, Kalser M H Arteaga, L, Yawn, E., Frazier D Leite C. A Ah am D G & Roth F Microbial intestinal flora in acute diarrheal disease. JAMA *201* 835, 1967

35. Cooper M L, Kell H M Walters, E. W Partin, J C. & Boye D E. Isolation of enteropathogenic *Escherichia coli* from mothers and newborn infants. Amer J Dis Child 97 255, 1959

36 Cooper R G Systemic *Pseudomonas* infection in childhood Med J Aust, *54* 527 1967

37 Cornelison, J L, Johnson, E. A. & Fischer W M Bacteriology of the oronasal cavity of the newborn Amer J Obstet Gynec, *52* 797 1946

38. Cozzi F & Wilkinson A W Oesophageal atresia Lancet, *II* 1222, 1967

39 Crem H & Saide C. *Pseudomonas aeruginosa (Pyocyaneus)* Pneumonien bei Neugeborenen Arch Kinderheilk, *169* 138, 1963

40 Curtin J A Petersdorf R G & Bennett, I L, Jr *Pseudomonas* bacteremia. Review of 91 cases. Ann Intern Med *54* 1077 1961

41 *Darrell J H & Wahba, A H Pyocine-typing* of hospital strains of *Pseudomonas pyocyanea.* J Clin Path, *17* 236, 1964

42 Dogget R. C Harrison G M Stillwell R. N & Wallis, E. S. Atypical *Pseudomonas aeruginosa* associated with cystic fibrosis of the pancreas. J Pediat *68* 215, 1966.

43 Dons, N Eriksen K. R & Jörgensen, S. Apparatur til ilterapi som infektionskild Ugeskr Laeg *121* 1525 1959

44 Dugdale, A. E., Harper J & Tierman, J R. Colonization of the neonate with staphylococci and gram-negative bacilli Acta Paediat Scand *56* 455, 1967

45 Edmondson, E. B Reinarz, J A, Pierce, A. K & Sanford, J P Nebulization equipment. A potential source of infection in gram-negative pneumonias. Amer J Dis Child, *111*:357 1966.

46. *Eggers, H. & Wockel, W* Zur Klinik und Pathologie der Pyocyaneusinfektion bei Frühgeborenen und Säuglingen. Deutsch Med Wschr *83* 174 1958.

47 Ensign P R. & Hunter C. A. An epidemic diarrhea in the newborn nursery caused by a milkborne epidemic in the community J Pediat, 29 620, 1946

48. Fairchild, J P Graves, C. D Vogel, E. H. & Ingersoll R. J Flora of the umbilical stump. J Pediat, *53*:538, 1958.

49 Farber S. & Vawter G F Clinical pathological conference. J Pediat, *62*:282, 1963.

50. Farber S. & Vawter G F *Pseudomonas* septicemia. Clinical pathological conference J Pediat *69* 485, 1966.

51 Feingold D S. & Oski, F *Pseudomonas* infection Treatment with immune human plasma. Arch Intern Med (Chicago) *116* 326, 1965.

52. Fetzer A E., Werner A. S., Hagstrom, J W C. Pathologic features of *Pseudomonal* pneumonia. Amer Rev Resp Dis, *96* 1121 1967

53. Finland M Jones, W F Jr & Barnes, M W Occurrence of serious bacterial infections since introduction of antibacterial agents. JAMA, *170* 2188 1959

54 Florman A. L. & Schifrin, N Observations on a small outbreak of infantile diarrhea associated with *Pseudomonas aeruginosa*. J Pediat, *36* 758, 1950

55. Forkner C. E., J *Pseudomonas aeruginosa infections* Grune & Stratton New York 1960.

56 Fisher C. E., J Frei, E. Edcomb, J H. & Utz. J P *Pseudomonas* septicemia. Observations of 23 cases Amer J Med *25* 877 1958.

57 Franklin, H C. & Loeb L. A Bacterial flora ... its encountered at the time of delivery. Study of 100 cultures from ... Amer J Obstet Gynec *56* 738, 1948.

58 Georgiade N Lucas, A Georgiade, R. & Garrett, W The use of new potent topical antibacterial agent for the control of infection in the burn wound Plast Reconstr Surg *39* 349, 1967

59 Geppert L. J Baker H J Copple B J & Pulaski, E. J *Pseudomonas* infections in infants and children J Pediat *41* 555, 1952

60. Clark L, Wood H F & Fousek, M D Septicemia of the newborn Pediat Clin N Amer *13* 1131 1966.

61 Gould, I. C. *Pseudomonas pyocyanea* infections in hospital. *In* R. E. O. Williams & R. A. Shooter (eds) *Infection in hospitals*. Davis, Philadelphus 1963, pp. 119–130

62 *Grönroos*, J. A. Palva, T & Saloheimo, M. Bronchoscopic observations in pulmonary tuberculosis, with special reference to cytologic and bacterial findings. Acta Tuberc Scand, *32*:165, 1956

63 *Hallow* F D Netzer E & Rubin, M I Penicillin and its effect in producing predominant gram-negative bacillary flora in upper respiratory tract of children. *Pediatrics*, *6*:262, 1950.

64 Hallstrom, K. *Desinfektionsaineiden käyttö sairaalassa* (Use of disinfectants in hospital.) Suom Laak, 22:2340, 1967

65 Haselhuhn, D H, Brason, F W & Borick, P M. The study of buffered glutaraldehyde for cold sterilization of anesthesia equipment. Anesth Analg (Cleveland), 46:468, 1967

66 Hatt, J I & Prinot, M. Affections à pyocyanique du nouveau-né et l'enfant 8 observations. Pediatrie, 18:975, 1963

67 Hitchings, G. H & Elion, G. B. Chemical suppression of the immune response. Pharmacol Rev *15*:367 1963.

68 Hobbs, J R. & Davis, J A. Serum γ-G-globulin levels and gestational age in premature babies. Lancet, *I*:757 1967

69 Hoffman, M A. & Finberg, L. *Pseudomonas* infections in infants associated with high *humidity en vironments*. J Pediat, *46*:626, 1955.

70 Horst, V & Sutter V L. Survival of *Pseudomonas aeruginosa* in the hospital environment. J I fect Dis, *116*:151 1966

71 Isoaho, E. Anestesia alaisesta aiheuttaman infektion torjunta (The prevention of infection caused by anesthetic equipment) Duodecim, *83* 6, 1967

72 Jacobs, J The investigation of an outbreak of *Pseudomonas aeruginosa* in pediatric wards. Postgrad Med, *40*:590, 1964

73 Jao, R L & Jackson, G G. Gentamicin sulfate, new antibiotic against gram-negative bacilli. Laboratory pharmacological and clinical evaluation JAMA, *189*:817 1964

74 Jedličková, Z & B ö, M Zum Problem der Antibiotikakombinationen bei *Pseudomonas aeruginosa in vitro* Z Ges Inn Med, *22*:215, 1967

75 Johnston, R B., J & Sell, S H. Septicemia in infants and children. Pediatrics, *34*:473, 1964

76 Jones, R J & Lowbury E. J L. *Susceptibility* of man to *Pseudomonas aeruginosa*. Preliminary communication. Lancet, *II*:623, 1965.

77 Kalmár, P & Ott, H. *Pyocyaneus*-Meningitis. Deutsch Med Wschr *87*:590, 1962.

78 Kalser, M H, Cohen, R., Arteaga, L, Yawn, E., Mayoral, L, Hoffert, W R. & Frazier, D. Normal viral and bacterial flora of the human small and large intestine. New Eng J Med, *274* 500, 1966.

79 Kangos, J J Septicemia in infancy The incidence of associated congenital anomalies. Arch Pediat, *67*:99, 1950.

80. Kauffmann, F *Enterobacteriaceae.* Ejnar Munksgaard, Copenhagen 1954, 2nd ed.

81. Kefalides, N A., Arana, J A., Bazan, A., Velarde, N. & Rosenthal, S. M., Evaluation of antibiotic prophylaxis and gammaglobulin, plasma, albumin and saline-solution therapy *in severe* burns. *Ann Surg*, *159*:496, 1964

82. Kenny, J F Boesman, M L & Michaels, R. H., Bacterial and viral coproantibodies in breastfed infants. Ped *iatrics*, *39*:202, 1967

83. Keown, K. K Gilman, R. A. & Bailey C. P., Open heart surgery Anesthesia and surgical experiences. JAMA, *165*:781 1957

84 Kislak, J W Eickhoff, T C. & Finland, M., Hospital-acquired infections and antibiotic usage in the Boston City Hospital. New Eng J Med, 271:834 1964.

85. Knights, H. T & Harvey J Hand creams containing hexachlorophene and cross infections with gram negative bacteria. New Zeal Med J *63*:653, 1964.

86 Kortekangas, A. E. In *vestigations* of the bacterial flora of the respiratory tract. Acta Otolaryng (Stockholm), suppl. 150, 1959.

87 Kortekangas, A. E. Otitis media ac. Duodecim, *80* 486, 1964

88. Kouvalainen, K. Gammaglobuliini terapeuttisena ja profylaktisena lääkeaineena (Gammaglobulin as therapeutic and prophylactic drug). Duodecim, *82* 479, 1966.

89 Kresky B. Control of gram-negative bacilli in hospital nursery Amer J Dis Child, *107*:363, 1964

90. Lányi, B Gregács, M. Ádám, M. M. Incidence of *Pseudomonas aeruginosa* serogroups in water and human faeces. Acta Microbiol Acad Sci Hung, 67:318, 1966.

91. Laurenzi, G. A., Potter R. T & Kass, E. H., Bacteriologic flora of the lower respiratory tract. New Eng J Med, *265*:1273, 1961

92 Laurell, H. Incidence of *Pseudomonas aeruginosa* and other gram-negative rods in newborn infants. Acta Obstet Gynec Scand, *41*:254, 1962.

28. Brumfitt, W Percival, A. & Leigh D A. Clinical and laborat ry studies with Carbenicillin. A new penicillin active against *Pseudomonas pyocyanea*. Lancet, *I* 1289 1967
29. Burns, M. W & May J R. Bacterial precipitins in serum of patients with cystic fibrosis. Lancet, *I* 270, 1968.
30. Caselitz, F H *Pseudomonas Aeromonas und u re humanmedizinische Bedeutung* VEB Gustav Fischer Verlag Jen 1966.
31. Cason, J S & Lowbury E. J L. Prophylactic chemotherapy for b rns. Lancet, *II* 501 1960
32. Cason, J S. & Lowbury E. J L. Mortality and infection in extensi ely burned patients treated with silve nitrate compresses. Lancet, *I* 651 1968.
33. Cocchi P & M rianelli L. Phagocytosis and intracellular killing f *Pseudomonas aeruginosa* in praematu e infants. Helv P ediat Acta, *22* 110 1967
34. Cohen R., K lser M. H Arteaga, I Yawn E., Frazier D Lelt C. A., Ahearn D G & Roth, F Microbial intestinal flora in acute diarrheal disease. JAMA, *201* 835, 1967
35. Cooper M L Keller H M Walters, E. W Partin J C. & Boye, D E Isolation f ent ropathogenic *Escherichi coli* from mothers and newborn infants. Amer J Dis Child, *97* 256, 1959
36. Cooper R. G Systemic *Pseudomonas* infection in childhood. Med J Aust, *54* 527 1967
37. Cornelison, J L., Johnson E. A & Fischer W M Bact ri logy f the oronasal ca ity of the newborn. Am J *Obst* t Gynec, *52* 797 1946
38. Cozzi, F & Wilkinson, A. W Oesophageal atresia. Lancet, *II* 1222, 1967
39. Gremer H & Sand C. *Pseudomonas aeruginosa (Procyaneus)* Pneumonien bei Neugeborenen Arch Kinderheilk, *169* 158, 1963.
40. Curtin, J A Petersd rf R G & Bennett, I L. Jr *Pseudomonas* bact emia Review of 91 cases. Ann Intern Med *54* 1077 1961
41. Darrell, J H & Wahba, A. H Pyocine-typing of hospital strains f *Pseudomonas pyocyanea*. J Clin Path *17* 236 1964
42. Dogget, R. G Harrison, G M Sullwell R. N & Wallis, E. S Atypical *Pseudomonas aerug n osa* associated with cystic fibrosi of the pancreas J Pediat *68* 215, 1966.
43. Dons, N Enkse K R & J gensen, S Apparatu til iltterapi so inf ktionskild Ugeskr Laeg *121* 1525, 1959
44. Dugdale, A. E H rpo J & Ti man, J R. Col nization f the neon te w th staphylococci and gram n gative bacilli Acta P edi t Scand *56* 155, 1967
45. Edmondson, E. B Reinarz, J A., Pierce A. K. & Sanford, J P Nebulization equipment. A potential source of infect on n gram negative pneu monias. Ame J Dis Child, *111* 357 1966.
46. Egg rs, H. & Wöckel, W Zur Klin k und Pathologie der Pyocy neusinfektion bei Fruhgeborenen und Säuglingen. Deutsch Med Woch *83* 171 1958.
47. Ensign, P R. & H nter C. A. An epidemic di rrhea in the newborn nursery caused by a m ikborne epidemic in the community J Pediat, *29* 620, 1946.
48. F irchild, J P Gravet, C D Vogel, E. H. & Ingersoll, R. J Flora of the umb lical stump. J Pediat, *53* 538, 1958.
49. Farber S & V wter G F Clinical pathological conference. J Pedi t, *62* 282, 1963.
50. Farber S & Vawt C F *Pseudomonas* septicemia. Clinical p th logical conference. J Pedi t, *69* 485, 1966.
51. Feingold D S & Oski F *Pseudomonas* nfection Treatment with im mune human plasma Arch Intern Med (Chicago) *116* 326, 1965.
52. Fetzer A. E., Werner A. S., Hagstrom, J W C. P thologic features of *Pseudomonal* pneumonia. Am r Rev Resp Dis, *96* 1121 1967
53. Finland, M., Jones, W F J & Barnes, M. W Occurrence of serious bacterial infections since introducti n of antibacterial agents. JAMA, *1 0* 2188, 1959
54. Florm n, A L & Sel ifrin, N Observations on a small o tbreak of infantil d arrhea associated with *Pseudomonas aeruginosa* J Pediat, *36* 758, 1950
55. F rkner C E., J *Pseudomonas aeruginosa infect ons*. Grune & Stratton, New Y rk 1960
56. F kner C. E., Jr Frei, E. Edcomb J H & Utz J P *Pseudomonas* septicemia. Observations of 23 cases. Amer J Med, *5* 877 1958
57. Franklin H C. & Loeb, L. N Bacterial flora in infants encountered t the t me f deli ery Study f 100 ultures f m lida. Amer J Obst t Gynec *56* 738, 1948.
58. Georgi de, N Lucas, N Georgi d R. & Garrett W The use f ew potent topical anti bact rial agent f th control f infection in the b rn wound Plast Reconst S rg, *39* 319, 1967
59. Geppert I J B ke H J Copple B J & Pulask E J *Pseudomonas* infections i infant and h ldren J Pedi t *41* 555 1952.
60. Gluck, L Wood, H F & Fouseck M D Septi cem f the newborn Pediat Clin N Amer *13* 1131 1966.

125 Phillips, I. & Spencer, G. *Pseudomonas aeruginosa* cross-infection. Lancet, *II* 1325, 1965.

126 Phillips, I., Lobo, A. Z., Fernandes, R. & Gundara, N. S. Acetic acid in the treatment of superficial wounds infected by *Pseudomonas aeruginosa*. Lancet, *I* 11, 1968.

127 Plotkin, S. A. & Austrian, R. Bacteremia caused by *Pseudomonas sp.* following the use of materials stored in solutions of a cationic surface-active agent. Amer J Med Sci, *235* 621, 1958.

128 Pommeren, C. A. *Pyocyaneus*-Hospitalismus auf einer Neugeborenenstation. Deutsch Med Wschr, *89* 1505, 1964.

129 Pryles, S. V., Lüders, D. & Alkan, M. K. A comparative study of bacterial cultures and colony counts in paired specimens of urine obtained by catheter versus voiding from normal infants and infants with urinary tract infection. Pediatrics, *27* 17, 1961.

130 Pyrah, L. N., Goldie, W., Parsons, F. M. & Raper, F. P. Control of *Pseudomonas pyocyanea* infection in a urological ward. Lancet, *II* 314, 1955.

131 Quincke, G. Über die Resistenzbestimmung an *Pseudomonas aeruginosa*-Stämmen gegen Colistin. Deutsch Med Wschr, *43* 2044, 1964.

132 Rantasalo, I. & Hjelt, L. Bacteriological findings in pneumonia of children. Ann Paediat Fenn, *9* 73, 1963.

133 Rantasalo, I. Antibiotic therapy of prematures. Acta Paediat Scand, suppl. *159* 55, 1965.

134 Reinarz, J. A., Pierce, A. K., Mays, B. B. & Sanford, J. P. The potential role of inhalation therapy equipment in nosocomial pulmonary infection. J Clin Invest, *44* 831, 1965.

135 Ricketts, C. R., Squire, J. R. & Topley, E. Human skin lipids with particular reference to the self-sterilising power of the skin. Clin Sci, *10* 89, 1951.

136 Rosenthal, S. M., Milligan, C. & Burt, J. A. A factor in human gammaglobulin preparations active against *Pseudomonas aeruginosa* infections. Proc Soc Exp Biol Med, *94* 214, 1957.

137 Ross, P. W. A new disinfectant. J Clin Path, *19* 318, 1966.

139 Rubbo, S. D., Gardner, J. F. & Franklin, J. C. Source of *Pseudomonas* in premature infants. J Hyg (Lond), *64* 121, 1966.

140 Sanford, J. P. Hospital acquired urinary tract infections. Ann Intern Med, *60* 903, 1964.

141 Sanford, J. P. & Barnett, J. A. Immunologic responses in urinary tract infections. JAMA, *192* 587, 1965.

142 Sarkany, I. & Gaylarde, C. C. Skin flora of the newborn. Lancet, *I* 589, 1967.

143 Schaffer, A. J. *Diseases of the newborn*. W. B. Saunders Company, Philadelphia, London 1965, 2nd ed.

144 Schergens, E., von Muralt, G., Butler, R., Heumann, G. & Gebert, J. Immunologische Probleme beim Frühgeborenen. Acta Paediat Acad Sci Hung, 7 213, 1966.

145 Schiøtt, C. R. & Stenderup, A. Terramycin-, Aureomycin og Chloromycetinafhaengige bakterier isoleret fra patienter. Ugeskr Laeg, 116 56, 1954.

146 Sever, J. L. Possible role of humidifying equipment in spread of infections in the newborn nursery. Pediatrics, 24 50, 1959.

147 Shinefield, H. R., Wilsey, J. D., Ribble, J. C., Boris, M., Eichenwald, H. F. & Dittmar, C. Interactions of staphylococcal colonizations. Amer J Dis Child, *111* 11, 1966.

148 Shooter, R. A., Walker, K. A., Williams, V. R., Horgan, G. M., Parker, M. T., Asheshov, E. H. & Bullimore, J. F. Faecal carriage of *Pseudomonas aeruginosa* in hospital patients. Possible spread from patient to patient. Lancet, *II* 1331, 1966.

149 Smith, J. W. & Bloomfield, A. L. The development of the aerobic bacterial flora of the throat in newborn babies. J Pediat, *16* 31, 1930.

150 Smith, R. T., Platou, E. S. & Good, R. A. Septicemia of the newborn. Pediatrics, *17* 549, 1956.

151 Speirs, C. F., Selwyn, S. & Nicholson, D. N. Hypogammaglobulinemia presenting as *Pseudomonas* septicemia. Lancet, *II* 11, 1963.

152 Stark, D. C. C., Green, C. A. & Pask, E. A. Anaesthetic machines and cross-infection. Anaesthesia, *17* 12, 1962.

153 Stratford, B. C., Clark, R. R. & Dixon, S. The disinfection of anaesthetic apparatus. Brit J Anaesth, *36* 471, 1964.

154 Stratford, B., Gallus, A. S., Matthiesson, A. M. & Dixon, S. Alteration of superficial bacterial flora in severely ill patients. Lancet, *I* 68, 1968.

155 Struwe, F. E. Beitrag zur Kenntnis der Infektionen mit *Pseudomonas aeruginosa (B. pyocyaneum)* im Säuglingsalter. Hel Paediat Acta, *19* 127, 1964.

156 Sulamaa, M., Paavola, M. & Louhimo, I. Imeväisten thoraxkirurgia. (Thoracic surgery in infancy.) Duodecim, *82* 491, 1966.

157 Summerlin, W. T. & Artz, C. P. Gentamicin sulfate therapy of experimentally induced *Pseudomonas* septicemia. J Trauma, 6 233, 1966.

158 Sussman, M. & Stevens, J. *Pseudomonas pyocyanea* wound infection. Lancet, *II* 734, 1960.

93 Legler F & Zeitle G Die Dünn- und Dick darmflora bei igen gastrointestinalen Krank heitsb ldern Deutsch Med Wschr 89 1506, 1964
94 Linde, K., Koeditz, H. & Kittlick, M Unter suchungen zur Frage der Säuglingsenteritis d urch *Pseudomonas aeruginosa (Pyocyaneus* Bakteria) Mschr Kinderhe lk. *110* 62, 1962
95 Linton, K. B & George E. Inactivation of chlorhexidine ("H bitane") by bark corks. Lancet, *I* 1553, 1966.
96 Loeschke, A & Ballowitz, L. Verhütun g von Inf kt onen beim Neugeborenen und auf Neugeborenenabteilungen. Mschr Ki derheilk, *113* *109* 1965.
97 Lo e, G J G son H M, Th mpson, D J Rog rs, K. D & Hatch, T F Rel tion of l ter ilty f st phylococcal i fection in newborn infants to contan ination f nurses hands and surrounding environment. Pedi trics, *32* 956, 1963.
98 Lowb ry E. J L. Contamination f cetrimide an d oth r flu ds witl *Pseudomonas pyocyanea.* Brit J Industr Med, *8* 22, 1951
99 Lowbury E. J L. & Fox, J Ep d miology of infection witl *Pseudomonas pyocyanea* in burns unit. *J Hyg (Camb) 52* 403 1954
100 Lowbury E. J L., Lilly H A. & Bull J P Disinfection f hands. Removal of transient r gan sms. Brit Med J 2 403, 1964
101 Lo bury E. J L. & Jackson, D M. Local l emoprophylaxis f r burns w th Gentamicin and ther gents. Lancet *I* 654 1968.
102. Lystad A. & Gardborg O Quantitative bacteriol gical examin tion of urin in children with rinary tract i fections A t Paediat Scand, *52* 277 1963.
103. MacDade, J J & Hall L. B Survi al f gramnegat bacteri in the environment. I Effect f rel ti hun id ty n surface-exposed rgan isms. Amer J Hyg 80 192, 1964
104 MacPherson, C R Oxygen-therapy — an un suspected source f hospital infection? JAMA, *167* 1083, 1958
105. McCurdy R. S & \ ter E. The effect f penicillin an d broadspectrum ant biotics on tl e emergence of gra n-n gati bacillary fl ra in th upper respirat y tract f i fant Ped atrics, 9 572, 1952.
106 McLeod J W Tl losp t l urine bottle d bedpan as reserv ir f infection by *Pseudomonas pyocyanea* Lancet, *I* 391 1958.
107 Mårtenson E H. Luftbakt riehalten på en operationsa del ig dersokt med sedimentorings platt Nord Med *64* 40 1960.
108 Miller A Gillespie, W A Li ton, K. B Seade V & M tchell, J P Postoperative in fecti n in urology Lancet, *II* 608, 1958.
109 Mitcl ell, R. G & H yward, A. C. Postoperative urinary tract infections caused by contam inated irrigating fluid. Lancet, *I* 793, 1966.
110. Moffet H. L. & Williams, T Bacteria recovered from distilled water and inhalation therapy equipment. Amer J Dis Child, *114* 7 1967
111 Moffet, H L., Allan D & Williams, T Survival and dissemination of bacteria in nebulizers and incubat rs. Amer J Dis Child, *114* 13, 1967
112. Moffet, H. L. & Allan, D Colonization of infants exposed to bacterially contaminated mists. Am J Dis Ch ld, *114* 21 1967
113 Monnet, P Chassignol, S. & Vailland, J E. Infections à *Pseudomonas aeruginosa* dans un centre de prématurés durant les années 1960 à 1963. A h Franç Pediat, *24* 543, 1967
114 Moore B & Forman, A. An outbreak of urin ry *Pseudomonas aeruginosa* infection acquired during urologi al operation Lancet, *II* 929 1966.
115. Nachtigal D & Feldman, M. Immunological unresponsiveness t protein antigens in rabbits e posed to x irradiation 6-mercaptopurine t tment. Immunology 6 356, 1963.
116. Note E. & Weintraub D H. An epidemi ologi study on *Pseudomonas (B. pyocyaneus)* in praem t re infants in the presence and absence of infection. J Pediat, *46* 280, 1955.
117 Noble, W C. & Savin J A. Steroid crean cont min ted with *Pseudomonas aeruginosa* Lancet, *I* 347 1966.
118. Nyhan, W L & Fousek, M. D Septicemia of the ewborn Pediatrics, 2 268, 1958.
119 Ocklitz, H. W & Schm dt, E F Enteropathogen *Escl erichia coli* serotypes Infection f newborn through mother Brit Med J 2 1036, 1957
120 Ogden A. E. & Rathmell, T K. Infections and benzalk un solutions. JAMA, *193* 978, 1965.
121 Olding L. Bacterial infection in cases of peri natal death. A m rphological and bacteriological study based on 264 topsies. Acta Paedi t Scand, supl 171 1966.
122. Pal a, T Kroonunen al korvan t lehdus. (Chronic t tis media.) Duodecim, *80* 190 1964
123 P ul. B & M get W *Pseudomonas-aeruginosa* Inf ktionen (Pyocyaneu Infektionen) des Säugl gs nd Kle nkindes. Deutsl Med Wsch *34* 1638, 1963
124 Pl ill ps, I Postoperati resp rat ry tract infec tion w tl *Pseudomonas aeruginosa* due t con t mi ted I gnocain jelly Lancet *I* 903,1966.

125. Phillips, I. & Spencer, G. *Pseudomonas aeruginosa* cross-infection. Lancet, *II* 1325, 1965.

126. Phillips, I., Lobo, A. Z., Fernandes, R. & Gundara, N. S. Acetic acid in the treatment of superficial wounds infected by *Pseudomonas aeruginosa*. Lancet, *I* 11, 1968.

127. Plotkin, S. A. & Austrian, R. Bacteremia caused by *Pseudomonas* sp. following the use of materials stored in solutions of a cationic surface-active agent. Amer J Med Sci, *235* 621 1958.

128. Primavesi, C. A. *Pyocyaneus*-Hospitalismus auf einer Neugeborenenstation. Deutsch Med Wschr *89* 1505, 1964.

129. Pryles, S. V., Luders, D. & Alkan, M. K. A comparative study of bacterial cultures and colony counts in paired specimens of urine obtained by catheter versus voiding from normal infants and infants with urinary tract infection. Pediatrics, 27 17 1961

130. Pyrah, L. N., Goldie, W., Parsons, F. M. & Raper F. P. Control of *Pseudomonas pyocyanea* infection in a urological ward. Lancet, *II* 314, 1955

131. Quincke, G. Über die Resistenzbestimmung von *Pseudomonas aeruginosa*-Stämmen gegen Colistin. Deutsch Med Wschr *41* 2044 1964

132. Rantasalo, I. & Hjelt, L. Bacteriological findings in pneumonia of children. Ann Paediat Fenn. 9 75, 1963.

133. Rantasalo, I. Antibiotic therapy of prematures. Acta Paediat Scand. suppl *159* 3, 1965.

134. Reinarz, J. A., Pierce, A. K., Mays, B. B. & Sanford, J. P. The potential role of inhalation therapy equipment in nosocomial pulmonary infection. J Clin Invest, 44 831 1965

135. Ricketts, C. R., Squire, J. R. & Topley, E. Human skin lipids with particular reference to the self-sterilizing power of the skin. Clin Sci, 10 89 1951

136. Rosenthal, S. M., Milligan, C. & Rust, J. A. A factor in human gammaglobulin preparations active against *Pseudomonas aeruginosa* infections. Proc Soc Exp Biol Med 94 214, 1957

137. Ross, P. W. A new disinfectant. J Clin Path, *19* 318 1966

138. Rubbo, S. D., Gardner, J. F. & Franklin, J. C. Source of *Pseudomonas* in premature infants. J Hyg (Lond) *64* 121 1966.

139. Sanford, J. P. Hospital acquired urinary tract infections. Ann Intern Med, 60 903, 1964

140. Sanford, J. P. & Barnett, J. A. Immunologic responses in urinary tract infections. JAMA, *1* 587 1965

141. Sarkany, I. & Gaylarde, C. C. Skin flora of the newborn. Lancet, *I* 589 1967

142. Schaffer, A. J.: *Diseases of the newborn*. W. B. Saunders Company, Philadelphia, London 1965, 2nd ed.

143. Schergoma, E., von Muralt, G., Butler, R., Hermann, G. & Gelsert, J. Immunologische Probleme beim Frühgeborenen. Acta Paediat Acad Sci Hung, 7 215, 1966.

144. Schutt, C. R. & Stenderup, A. Terramycin-Aureomycin- og Chloromycetinafhængige bakterier isoleret fra patienter. Ugeskr Laeg, *116* 56, 1954.

145. Sever, J. L. Possible role of humidifying equipment in spread of infections in the newborn nursery. Pediatrics, *24* 50, 1959.

146. Shinefield, H. R., Wilsey, J. D., Ribble, J. C., Boris, M., Eichenwald, H. F. & Dittmar, C. Interactions of staphylococcal colonizations. Amer J Dis Child, *111* 11, 1966.

147. Shooter, R. A., Walker, K. A., Williams, V. R., Horgan, C. M., Parker, M. T., Asheshov, E. H. & Bullimore, J. F. Faecal carriage of *Pseudomonas aeruginosa* in hospital patients. Possible spread from patient to patient. Lancet, *II* 1331, 1966

148. Smith, J. W. & Bloomfield, A. L. The development of the aerobic bacterial flora of the throat in newborn babies. J Pediat, *36* 51 1950

149. Smith, R. T., Platou, E. S. & Good, R. A. Septicemia of the newborn. Pediatrics, 17 549 1956.

150. Spears, C. F., Selwyn, S. & Nicholson, D. N. Hypogammaglobulinaemia presenting as *Pseudomonas* septicemia. Lancet, *II* 711 1965.

151. Stark, D. C. C., Green, C. A. & Pask, E. A. Anaesthetic machines and crossinfection. Anaesthesia, *17* 12, 1962.

152. Stratford, B. C., Clark, R. R. & Dixon, S.: The disinfection of anaesthetic apparatus. Brit J Anaesth, *36* 471, 1964

153. Stratford, B. C., Gallus, A. S., Matthiesson, A. M. & Dixon, S. Alteration of superficial bacterial flora in severely ill patients. Lancet, *I* 68, 1968.

154. Struwe, F. E. Beitrag zur Kenntnis der Infektionen mit *Pseudomonas aeruginosa (B. pyocyaneum)* im Säuglingsalter. Helv Paediat Acta, *19* 127 1964

155. Sulamaa, M., Paala, M. & Louhimo, I.: Imeväisten thoraxkirurgia. (Thoracic surgery in infancy.) Duodecim, *82* 191 1966.

156. Summerlin, W. T. & Artz, C. P. Gentamicin sulfate therapy of experimentally induced *Pseudomonas* septicemia. J Trauma, 6 233, 1966.

157. Sussman, M. & Stevens, J. *Pseudomonas pyocyanea* wound infection. Lancet, *II* 734 1960.

93. Legler F & Zeitler G Die Dünn nd Dick dau nfl be einigen gastrointestinal i krank heitsl ildern Deutsch Med Wschr 89 1506, 1964
94 Linde K., Koeditz, H & Kittlick, M Unter suchungen zur Frage der Säuglingsenteritis durch *Pseudomonas aeruginosa (Pyocyaneus-*Bakteri) Mschr Kinderheilk. *110*·62 1962.
95 Linton K. B & George, E. Inactiv tion of chlo hexid o ("H bitane") by bark corks. Lancet *I* 1353, 1966.
96 Loeschke, A & Bollowitz, L. V hutung von Infektionen be m Neugeborenen und f Neu geborenen btellungen. Mschr Kinderheilk, *113* 109 1965
97 Love G J G ron H M., Tl mpso D J R gers, K. D & H tch, T F: Relation of intensity f staphylococcal infection in newborn infants t contamination of nurses h nds and surroundi g environ ent. Pediatrics, *3* 956, 1963.
98. Lowbury E. J L. Contamin t n of triu ide a d other fluids w tl *Pseudomonas pyocyanea.* Brit J Industr Med *8*:22, 1951
99 Lowbury E. J L. & Fox J Epidemiol gy of infection with *Pseudomonas pyocyanea* n burns unit. J Hyg (Camb), *5* 103 1954
100 Lowbury E. J L., Lilly H A & Bull, J P Disinfection of han ds. Remo al f transient g sm. Brit Med J 103, 1964
101 Lowbury E J L. & J kson, D M Loc l l emop phylaxis f r burn with Gentamicin and tl er agents. Lancet *I* 654 1968.
102 Ly t d, A & G rdborg O Quant t t bacteriolog cal ex m ation f e in hild en with inary t t i fections. A ta l aediat Scand, *5* 277 1963
103. MacDade J J & H ll L B Surv al f gram-gati e bacteria n th en i onment I Effect f relat ve hum dity surface-exposed orga is s Amer J Hyg *80* 192, 1964
104 Ma Ph rson C H. O ygen therapy — an unsuspected source f l osp tal infection JAMA, *16* 1083, 1958.
10 M C rdy R S. & Neter E. Tl ffect f penic ll n an l b oadspectru m ant i ties on th emergence of gra -neg ti bacill ry flo tl upper es} rat ry t ct f nf t Ped t cs, 9 572, 1952
106 M Leod J W Tl l sp t l ur bottl n d bedpan as reser rs f fection by *Pseudomonas pyocyanea* La t, *I* 391 1958.
107 Mårtenson F H Luftbakt rieh lten på en per tl sa del g dersökt med sedimenteringspl tt Nord M l *64* 10, 1960.
108. Miller A Gillesp e W L, Linton K. B Seade V & Mit hell, J P Postoperative nfection in urology Lanc t *II*·608, 1958.
109 M tchell R. G & Hayward, A. C. Postoperative urinary tract infections caused by contamin ted irrigating fluid. Lancet, *I* 793, 1966.
110 M ffet, H L. & Williams, T Bacteria recovered from distilled w ter and inhalation therapy equip ent. Amer J Dis Child, *114* 7 1967
111 Moff t H L., Allan D & W lliams, T Survival and dissemination f bacteri in nebulizers and i cubators. Amer J Dis Child, *114* 13, 1967
112. Moffet, H L. & Allan, D Colonization of infants exposed to bacterially contaminated mists. Amer J Dis Child *114*·21 1967
113. Monn t, I Chassignol, S. & Vailland, J E. Infect ons à *Pseudomonas aerugi osa* dans un cent o d prématu és durant les années 1960 à 1963. Arch Franç Pediat, *I* 313, 1967
114 Moore B & Forman, A. An outbreak f uri ary *Pseudomonas aerug nosa* infection acquired d u g urological perations. Lancet, *II* 929 1966.
115 Nachtgal D & Feldman, M. Immunological unresponsiveness t protein antigens n rabbits xposed to x irradi tion 6-mercaptopurine t tment. Imm unology *6* 356, 1963.
116 Net E. & Weintraub D H. An epidemiologic study on *Pseudomonas (B. pyocyaneus)* in prem tat re infants in the presence and bsence f nfection J Pedi t *46*.280, 1955
117 N ble W C. & Sa i, J A. Steroid cream co tami ated with *Pseudomonas aer ginosa* Lan t, *I* 347 1966.
118. Nyl an W L. & F uck, M D Septicemia f tl ew born. Ped at ics, 268, 1958.
119 Ocklitz H W & Schm dt E F Ent ropathogenic *Escl ri l ia col* serotypes. Infection f newbo through mother B it Med J 2 1036, 1957
120 Ogden A E. & Rathn ell, T K Infect ons and ben alk sol tions. JAMA, *193*.978, 1963
121 Oldi g L. Bacterial infection in cases f perital death A morphological and bacteriological tudy based on 964 topsies. Act Paed t Scan d u ppl 171 1966.
122 l al T kroonmer alikors n tulehdus (Cl ro l t t edi) Duodeci a, *80* 190 1964
123. I I R. & M rget W *Pseudomonas-aeruginosa*-I f ktion en (*Pyocyane* s-I f ktionen) des Sa gl gs d Klei ki les Deutsch Med Wsch *14* 1638, 1963.
124 Ph ll ps, I Post perati respi t ry tract infec th witl *Pseudomonas eruginosa* d ie t con t i ted Lignoc l j lly La cet *I* 903,1966.

159 Sutte V L., Hurst, V Grossman, M. & Calon je R. Source and significance of *Pseudomonas aeruginosa* in sputum Patients requiring tracheal suction JAMA, *197* 854 1966.

160. Thoburn, R F Koty F R., Jr Cluff L. E. & Melvin, V B Infections acquired by hospitalized patients. Arch Intern Med (Chicago) *121* 1 1968.

161 Tinne, J E., Gordon, A. M., Bain, W H. & Ma key W A. Cross-infection by *Pseudomonas aeruginosa* as a hazard f intensive surgery Brit Med J *4*:3375 1967

162. Toplitz, C., Da is, W Raulston, G Mason, A. & Moncrief J A. *Pseudomonas* burn wound sepsis. II Hematogenous infection at the junc tion f the burn wound and the unburnt epider mis. J Surg Res, *4*:212, 1964

163 T rrey J C. & Reese, M. K. Initial aerobic fl ra of infants. Ame J Dis Child, *69*:208, 1945.

164 Tun all, G Nosokokomial infection. I Routes f bacterial dissemination in hospitals. Nord Med *63* 37 1960

165. Victorin L. An epidemic of otitis in newborn di o to infection with *Pseudomonas aeruginosa*. Acta P edi t Scand, *56* 344 1967

166. Viola, M V Acute leucemia and infection. JAMA *201*:923, 1967

167 Wahba, A. H Hospital infection with *Pseudomonas pyocyanea*. Investigation by combined pyocine and serological typing method. Brit Med J *1* 86, 1965.

168. Waldton S Luftbakt riehalten på ett central lasaretts operationsa delning (speciellt under på gående operation) N rd Med, *64* 35, 1960.

169 Washburn, T C & Medearis, D N Jr & Childs, B Sex differences in suscept b lity to infections. Pediatrics, *35* 57 1965

170 Watanabe, T Infective heredity of multiple drug resistance in bacteria. Bact Rev 27 87 1963.

171 Waterston D J Carter R. E. & Aberdeen, E. Oesophageal atresia Tracheo-oesophageal fis t la. A study of survival in 218 infants. Lancet, *1* 819 1962.

172. Weil, M H Shubin, H & Biddle, M Shock caused by gram-negative micro-organisms. Analysis f 169 cases. Ann Intern Med, 60.384 1964

173. Widholm, O Hjelt L. & Cantell, K. The birth canal as the origin of primary infantile infections. Ann Med Exp Biol Fenn, *36* 191 1958.

174 Widholm, O Makitalo, R., Renkonen, O V & Ost rlund K. Bacterial contamination of the vagina during delivery Gynaecologia, *153* 37 1962.

175. Williams, R. E. O Blowers, R., Garrod, L. P & Shoot R. A. *Hospital infection. Causes and prevention*. Lloyd-Luke Ltd, London 1966, 2nd ed.

176. Williams, R., Williams, E. D & Hyams, D E. Cross-infection with *Pseudomonas pyocyanea*. Lancet, *1* 376, 1960.

177 Wilson G S. & Miles, A. A. *Topley and Wil son s Principles of bacteriology and immunity* Edward Arnold Ltd, London 1964 5th ed.

178. W lson, M. G Nelson, R. C., Phillips, L. H. & Boak, R. A. New source f *Pseudomonas* in a nursery JAMA, *175* 1146, 1961

179 Wingo-Heden, K. Bacteriological studies on anaesth tic pparatus. Acta Chir Scand *1 4* 294 1962.

180 Y w E. M Development f *Proteus* and *Pseudomonas* infections during antibiotic therapy JAMA *149* 1184 1952

181 Ziegler C & Jacoby J Anaesthetic equipment as a source of infection. Anesth Analg (Cleveland) *35* 451 1956.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 196 1969

SOCIAL AND PSYCHOLOGICAL FACTORS INFLUENCING HOSPITAL ADMISSION OF CHILDREN

BY GEORG ROSBERG

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

131. Mellbin, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw kr. 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw kr 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr. 25.— 1962
134. Müller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw. kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr. 25.— 1962
137 Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., *The Relation of Linoleic Acid to Infant Feeding. A Review.* Sw kr 25.— 1962
138. Wallgren, Eric Ivar Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw kr 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen, 1961, Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wern-Hückert, Ole and Dunner Mårta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study Sw. kr 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy A Clinical and Experimental Study Sw. kr. 25.— 1963
144. *Sterky Göran, Diabetic Schoolchildren.* Sw. kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply Sw kr 20.— 1963
149. Valaes, Timos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr 25.— 1963
150. Mee, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151 *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organisation of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw kr 15.— 1963
152. Hjern, Bo and Nylander, Ingvar Acute Head Injuries in Children Traumatology Therapy and Prognosis. Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study. Sw kr. 30.— 1964
155. Engström, Ingemar, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung V[illegible] and Ventilatory Capacity in Asthmatic Children fro[illegible] Symptom-free Status. Sw. kr
1964
[illegible] von R[illegible] on Paediatrics, Lis-
Bo Vahlq[illegible] Sw. kr 25.— 1964
[illegible] Kal[illegible] A., Obstructive Type
of [illegible] in Four Siblings. Sw kr.
1964
[illegible] Infant. Sw. kr. 25.—
[illegible] Paediatric Congress.
Sw kr 25.— 1965
[illegible] Disease in Sweden. Sw. kr.
[illegible] ical Studies on Fetal
20.— 1965

162. Landmark, Karl Martin, Bone Marrow Cell Health and in Haematological Disease during Childhood. kr 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.—
164. Böttiger, Margareta, Studies on Immunization with and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. Bronchiectasis: A Review of 187 Cases in Children with up Pulmonary Function Studies in 58. Sw. kr 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile toid Arthritis. Analysis of 544 Cases. Sw. kr 35.— 1966
167 Iversen, Torben, *Leukaemia in Infancy and Childhood.* A rial of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trolaborg, W Focal Spike [illegible] nal Study Sw kr 25.— 1966
169. Dahl, Matti, *Intracardiac Phonocardiography of the* in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, *Bacterial Infection in Cases of Perinatal D* morphological and bacteriological study Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chorenis.* Sw. kr. 15.—
173. Walsh, S. Zoe, The Esophageal [illegible] First Week of Life. Sw. kr 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum clinical study before and after operation with special to haemodynamic function. Sw. kr 25.— 1967
175. Hiltunen, Pentti, Vectorcardiographic Studies in fants. Sw kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Sw. kr. 20.— 1967
177 *Proceedings of the Fifteenth Northern Pediatric Congress.* 1967 Sw. kr. 35.— 1967
178. Ekegren, Irène, Echoencephalography in Special Regard to Measurement of the Ventricular Size. kr. 25.— 1967
179 *Quantitative Studies of the Human Neonatal Circulation.* by Göran Wallgren. Sw. kr 25.— 1967
180. Andersen, Hans Jürgen, *Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children* Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw kr 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A and Clinical Study. Sw kr 25.— 1968
183. Robertson, Alex F and Sprecher, Placental Lipid Metabolism and Transport. Sw. kr. 25.—
184. Robertson, Bengt, *The Intrapulmonary arterial pat* Infancy and in transposition of the great arteries. 1968
185. Andersen, Elsa, *Skeletal Maturation of Danish School* in Relation to Height, Sexual Development, and Social tions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome *of the Literature and Report of Nine Cases.* Sw
187 Karlberg, Petter *et al.*, The Development of Children in dish Urban Community A Prospective Longitudinal Study Sw kr 30.— 1969
188. Mossberg, Gunnar W., and Malis, Kerstin, Studies in Galactose Malabsorption. A Clinical Study of 6 Cases Genetic Study Sw kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 19
190. Hörnblad, P Yngve, Experimental Studies on Closure Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr 1969
191 Kaivitikia, Antti, Cardiovascular Response of the Neonat to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 1969
192. Vihma, Leena, *Surveillance of Acute Viral Respiratory* in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Groups at Risk in Low Birth and Perinatal Mortality. Sw. kr. 30.— 1969
194. Kamunto, Antti, Studies on the Serum Binding of [illegible] in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thern, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr 1969
196. Rosberg, Georg, Social and Psychological Factors Hospital Admission of Children with Special Reference to Disorders and Functional Symptoms. 1969
197 Samila, Ritva, Pseudomonas Infections in Paediatric Unit. Sw kr. 20.— 1969

20 —

Wiksells Boktryckeri AB Uppsala

ACTA
PÆDIATRICA
SCANDINAVICA

SUPPLEMENT 196 1969

SOCIAL AND PSYCHOLOGICAL FACTORS INFLUENCING HOSPITAL ADMISSION OF CHILDREN

BY GEORG ROSBERG

ALMQVIST & WIKSELL STOCKHOLM SWEDEN



Department of Pediatrics, University of Oulu
Children's Hospital, University of Helsinki

SOCIAL AND PSYCHOLOGICAL FACTORS INFLUENCING HOSPITAL ADMISSION OF CHILDREN

with special reference to mental disorders and functional symptoms

By

GEORG ROSBERG

Also published as Supplement No 196 of
Acta Paediatrica Scandinavica 1969

Liikekirjapaino Oy — Helsinki 1969

To my Parents



Contents

Introduction

Since the community must invest considerable capital in hospital buildings, staff salaries and equipment, it is important that hospital beds are used in accordance with conditions laid down for the operation of the hospital. A full understanding of all the reasons why patients are admitted and accepted for admission to hospital is thus important. For children in particular it has been found that admission to hospital cannot always be decided solely on purely medical indications. There are other contributory factors, chiefly social or psychological, or a combination of the two.

The general hospital system of Finland, especially the network of central hospitals, is being constantly enlarged. This requires huge investment. Certain important social considerations are associated at present with the problem of admissions: increasing gainful employment of the mother, home help facilities provided by the community, housing shortage and small size of homes etc. For these reasons, it was felt that the problem should be studied from the pediatric viewpoint for the whole country within the framework of a comprehensive research project.

When the collection of the present data was planned in 1962, some investigations had already been carried out in Finland into the effect of social factors and on the need for hospitalization of children (Rantasalo and Valpola 1955, Haavio-Mannila 1962 and Väänänen 1962). The intention was, however, in this study, to carry out a close, individual interview on the admission of each patient, complete with statements on discharge from the hospital. The study was launched by a research group and the collection of data was made possible by the kind co-operation of the chief pediatricians and their staffs from twenty-one Finnish pediatric units.

Some preliminary reports have been given from the data collected. Papers were presented at the International Pediatric Hospitalization Symposium in Paris in 1963 (29), at the International Congress of Pediatrics in Tokyo in 1965 (28) and at the first Scandinavian Congress of Social Medicine in Gothenburg in 1967 by Wasz-Höckert (8).

In the present study the social and psychological factors influencing the hospital admission of children have been analysed with special interest in mental disorders and functional symptoms in childhood. Other aspects have also been analysed and will be published later.

Introduction

Since the community must invest considerable capital in hospital buildings, staff salaries and equipment, it is important that hospital beds are used in accordance with conditions laid down for the operation of the hospital. A full understanding of all the reasons why patients are admitted and accepted for admission to hospital is thus important. For children in particular it has been found that admission to hospital cannot always be decided solely on purely medical indications. There are other contributory factors, chiefly social or psychological or a combination of the two.

The general hospital system of Finland, especially the network of central hospitals, is being constantly enlarged. This requires huge investment. Certain important social considerations are associated at present with the problem of admissions: increasing gainful employment of the mother, home help facilities provided by the community, housing shortage and small size of homes etc. For these reasons, it was felt that the problem should be studied from the pediatric viewpoint for the whole country within the framework of a comprehensive research project.

When the collection of the present data was planned in 1962, some investigations had already been carried out in Finland into the effect of social factors and on the need for hospitalization of children (Rantasalo and Valpola 1955, Haavio-Mannila 1962 and Väänänen 1962). The intention was, however, in this study, to carry out a close, individual interview on the admission of each patient, complete with statements on discharge from the hospital. The study was launched by a research group and the collection of data was made possible by the kind co-operation of the chief pediatricians and their staffs from twenty-one Finnish pediatric units.

Some preliminary reports have been given from the data collected. Papers were presented at the International Pediatric Hospitalization Symposium in Paris in 1963 (29), at the International Congress of Pediatrics in Tokyo in 1965 (28) and at the first Scandinavian Congress of Social Medicine in Gothenburg in 1967 by Wasz Höckert (78).

In the present study the social and psychological factors influencing the hospital admission of children have been analysed with special interest in mental disorders and functional symptoms in childhood. Other aspects have also been analysed and will be published later.

Review of the literature

a) SOCIO-PSYCHOLOGICAL ASPECTS OF HOSPITAL ADMISSION

In the last ten years there has been keen research especially in the USA, into the social and psychological reasons influencing the approach to community health resources. Many workers have studied the approach to hospitals out patient clinics, private practitioners and healers, and the reasons for taking this step

The studies have revealed that women visit hospitals more frequently than men and that the frequency increases among both sexes with age (99) It has also been shown that the utilization of health resources varies in direct proportion to the social class (48) Holders of health insurance policies use medical care facilities especially hospitals (14)

As a rule, these studies have sought to elucidate the social background factors in detail They have not explained why people seek medical advice, why some delay while others do not why some consult physicians and others go to healers The replies to these questions have been sought in various motivation studies, in which the medical behaviour of the public has been studied systematically A partial reason for the poor results achieved in the studies may be the evident difficulty of establishing objectively measurable quantities in human behaviour and its measurement in the socio-psychological field

One of the studies in this field that ranks as almost classical is that of Merril and co-workers (1958) on the attitudes of Californians to poliomyelitis vaccination They showed that friends, neighbours and the family doctor decided the issue.

Several other factors have also been found to influence the illness behaviour in the diseases of adults (1 23 25 45 47 48 50 52 63 71 85 86 93)

The wellknown English field study conducted under the supervision of Spence (1954) showed that there was no correlation between the socio-economic status of the family and the probability of hospital admission for the child But they found a distinct correlation between the child's hospital admission and maternal capacity A child whose mother could not manage to care for it was admitted to hospital twice as often as a child whose mother could look after it satisfactorily The authors considered the mother's ability to care for her child as the decisive factor governing the hospitalization of children On the other hand, this maternal factor was not important enough to produce a significant correlation with social class.

In many respects the book by Miller and co-workers (1960) was a continuation of Spence's work. Diseases in children were followed for 5 years and 20 4 per cent of the children were admitted to hospital at least once in the 5 years. After the first year a few children had repeated admissions, but there was no significant correlation of admission with the mother's capacity

One of the most complete and detailed studies of the influence of social and psychological factors on children's hospital admissions was the one carried out by Straus in 1961 among the population of Paris (92) He started from the observation that a considerable number of children were admitted to hospitals in Paris for commonplace diseases. The children were slightly ill, diagnosis produced no

difficulty no special examinations were performed on them and they received no therapy necessitating hospitalization. Straus made an effort to analyse the social and psychological factors affecting the hospitalization of these children.

He first considered the part played by the referring physician, and the decision of the hospital physician which was influenced by the number of beds available. In 65 per cent of the cases in which a child was admitted without the recommendation of a physician, social factors affected the admission. Especially when the child was repeatedly re-admitted a number of social or psychological factors lay in the background. When previous admissions among siblings were studied it was found that if a child had been admitted more than three times, one of its siblings had also been in hospital in 89 per cent of the cases, compared with 44 per cent for the general hospital patient material.

Straus found that housing conditions were the decisive social factor which is readily understandable in a city of the size of Paris, with its slums. One-room dwellings, casual lodgings and inadequate hygiene often led to the admission of children for social reasons. The influence of unfavourable housing was seen most distinctly in those groups admitted without a physician's recommendation, re admitted repeatedly and always for medically inadequate indications.

Of the other social background factors of the Parisian study it may be mentioned that the family father was often a casual labourer and the family's monthly income was low. These factors were often associated with the housing conditions.

Straus found that the mother's employment outside the home was often dictated by economic necessity and came to the conclusion that gainful employment combined with a large number of children is an important factor of social influence. The author also emphasized that job insecurity discouraged the mothers from staying at home to care for the child, and thus made them bring the child to hospital. Fifty per cent of the mothers employed outside the home entrusted their children to somebody else's care. This solution was almost inevitable when the woman was the sole breadwinner and housing conditions were poor. Among the children under institutional care, the incidence of direct efforts to gain hospital admission (without a medical recommendation) re-hospitalization, and admission on inadequate medical indications was significantly higher.

A review of the statements issued by physicians consulted casually and by the family doctor revealed that social factors were influential in 50 per cent of the former but only 25 per cent of the latter. Straus attributed this partly to the fact that the physician called in casually had not enough authority or hesitated to assume responsibility and was thus more readily inclined to send the child to hospital on his first visit, due to the social and psychological factors he saw.

Straus concluded that the mother's psychic inadequacy — often combined with difficult social conditions — led to the child's admission to hospital.

Another French study was that of Albon et al. (1961) on the background factors of 3,272 children with motor disabilities. In addition to geographical, social and medico-etiological differences, the variations between diagnostic groups were also considered.

Earlier some investigations have been undertaken in Finland on the use of hospital beds for children and the social factors influencing hospital admissions.

Rantasalo and Valpola (1955) established on the basis of their series of 2,151 children treated in the City Hospital of Helsinki, that social factors play a significant role in the hospital admission of children. A greater number of children from families in difficult social conditions were admitted than their proportion of the city population. When common infectious diseases and the age group 7—14 years were omitted, the difference was even more distinct. The role of social factors also appeared clearly in whether the children were admitted from home care or institutional care.

In his comparison of the social back

Review of the literature

a) SOCIO-PSYCHOLOGICAL ASPECTS OF HOSPITAL ADMISSION

In the last ten years, there has been keen research especially in the USA, into the social and psychological reasons influencing the approach to community health resources Many workers have studied the approach to hospitals out patient clinics, private practitioners and healers and the reasons for taking this step

The studies have revealed that women visit hospitals more frequently than men and that the frequency increases among both sexes with age (99) It has also been *shown that the utilization of health re* sources varies in direct proportion to the social class (48) Holders of health insurance policies use medical care facili ties, especially hospitals (14)

As a rule these studies *have sought to* elucidate the social background factors in detail They have not explained why people seek medical advice why some delay while others do not why some consult physicians and others go to hea lers The replies to these questions have been sought in various motivation stu dies in which the medical behaviour of the public has been studied systema tically A partial reason for the poor results achieved in the studies may be the evident difficulty of establishing objectively measurable quantities in hu man behaviour and its measurement in the socio-psychological field

One of the studies in this field that ranks as almost classical is that of Merril *and co-workers (1958) on the* attitudes of Californians to poliomyelitis vaccination They showed that friends, neighbours and the family doctor decided the issue.

Several other factors have also been found to influence the illness behaviour in the diseases of adults (1 23 25 45 47 48 50 52 63 71 85 86 93)

The wellknown English field study conducted under the supervision of Spence (1954) showed that there was no correla tion between the socio-economic status of the family and the probability of hospi tal admission for the child But they found a distinct correlation between the child s hospital admission and ma ternal capacity A child whose mother could not manage to care for it was ad mitted to hospital twice as often as a child whose mother could look after it satisfac torily The authors considered the moth er's ability to care for her child as the decisive factor governing the hospitali zation of children On the other hand this maternal factor was not important *enough to produce a significant correlation* with social class.

In many respects the book by Miller and co-workers (1960) was a continuation of Spence s work. Diseases in children were followed for 5 years and 20 4 per cent of the children were admitted to hospital at least once in the 5 years. After the first year a few children had repeated admissions, but there was no significant correlation of admission with the mother s capacity

One of the most complete and detailed *studies of the influence of social* and psychological factors on children s hospital admissions was the one carried out by Straus in 1961 among the population of Paris (92) He started from the observat ion that a considerable number of children were admitted to hospitals in Paris for commonplace diseases. The children were *slightly ill diagnosis* produced no

level and the intelligence level indicate the same trend. Inghe also points out that a partial explanation for the accumulation of mental disorders in the lower social classes is perhaps offered by the »down drift hypothesis» advocated particularly by Faris and Dunham (1939) in USA. This hypothesis claims that certain difficulties of adaptation before the illness, and in earlier generations, may result in the degradation of the social class. Inghe found that hereditary factors had received little attention in the studies to date. A long term sedimentation process may be assumed, with earlier generations, which carried the oligophrenic factors, having gradually become over represented in the lower stratum of society.

Stenbäck and Achté studied the correlation between mental disorders and social background in the city of Helsinki (1965 and 1966). In their study of the incidence of psychiatric diseases (1965) they analysed the first hospital admission of male patients and found that among 238 cases of psychosis the incidence was lowest in the highest social class. The lowest social class (IV) showed a significantly higher incidence of schizophrenia than the other classes. In their study (1966) of the social classes of 1216 male patients hospitalized for the first time, the same authors found that the age-adjusted annual rates of psychosis and neurosis revealed approximately the same incidence in social classes I, II and III. In the lowest social class the incidence was about twice that of the others. The incidence of schizophrenia was significantly lower in social class I than II. A parallel but not statistically significant difference was seen between classes II and III. The incidence of affective disorders was highest in social class I and lowest in class III.

The studies cited in the foregoing dealt with the correlation between social position and mental disorders in adults. Bearing in mind the stability of the classes in different generations in Finland (Allardt 1964) it may be assumed that the disorders might to some extent be reflected by social classes in children and especially in adolescents or teenagers. It may also be assumed, naturally, that the mental disorders of the parents are reflected in the children as environmental injuries or possibly hereditary damage.

Heredity has been discussed from this point of view e.g. by Kaila (1950) and Annell (1965). The conclusion reached was that although the mutual relationship of environmental and hereditary effects was very complicated, both mental retardation and psychiatric diseases were based on hereditary predisposition.

Srole and co-workers (1962) tried to throw light on the parental socio-economic background as related to the mental health of the offspring. He took as his basis that the social status of the parents provided a different starting point for the development of each individual, and this parental social status could be objectively measured. The authors found that the socio-economic position of the parents and the mental health of the offspring were positively correlated. But the role of the greater security enjoyed by the higher social classes for the mental health of the children was unclarified.

Eisenberg (1961) particularly emphasized the importance of prophylactic child psychiatry. He pointed out that the neuropsychiatric disorders were concentrated in slums. Disorders in the foetal central nervous system may, according to Eisenberg, result from malnutrition, inadequate prenatal treatment and difficulties of life subject to which the pregnant mother lives. The child's brain may suffer damage due to poor control of infections and the action of toxins. Furthermore, a slum child lives in an environment where it receives little mental stimulation.

In studying the factors which were responsible for children's mental disorders Söderling (1966), starting from common psychosomatic disorders, concluded that a school system, which is foreign to reality, may damage the child during the age of development. The complete indifference of higher institutes of learning to the personal problems of young people in puberty, the competition mentality and restrictions imposed on free thinking may in particular damage the

ground factors of children admitted to hospital in South and North Finland Väänänen (1962) showed that the number of children in the family the child's age the seniority of the child among the siblings the marital status of the parents, the size of the home the distance of the home from the hospital the financial standing of the family and the type of community are significant factors in deciding whether or not a child is admitted

Kuusi (1963) while discussing community health services in Finland emphasized that information should be obtained on the health of the population, incidence of diagnosable diseases, composition of patients treated in and outside hospitals consumers of various drugs, etc On the basis of this information efforts should be made to determine the demands upon various public health and medical services and to outline the future development of community health resources From the data available it seems obvious that the fundamental weakness in Finnish public health work is the patients delay in seeking medical advice, which is partly due to the shortage of available medical services in the country

Morbidity and the need for medical services have also been studied in Finland later (70 76 106)

Kantero and Sorvettula (1965) found that although some parents had read or listened to lectures on child care this did not seem to affect the precautions against anaemia among their children On the other hand interest in various public health problems appeared to be correlated with the readiness to take the child to hospital but not with the predisposition to illness

Hultin (1967) studied the influence of the social environment on the somatic development of the child in Finland paying attention to the fact that a difficult social milieu such as poor housing conditions and inadequate nutrition resulted in an increase of respiratory infections and hence an increased need of hospital services. The negative influence of the environment emerges most readily at the age of less than two years. The importance of the foetal period is also very great in poor social conditions On the other hand, a good socio-economic environment is no absolute guarantee of good health and sounder development Improved social environment and higher living standard may result in an increase of consumer goods, tobacco beverages, and technical auxiliaries all detrimental to health as living standards rise.

b) MENTAL DISORDERS AND HOSPITAL ADMISSION

Social epidemiology of mental disorders has been studied and two extensive investigations concerning adult patients have arrived at apparently different results. Hollingshead and Redlich (36) in 1958 divided the population into five social classes according different weights to the place of residence the occupation and the education of the head of the family but weighting education most heavily A comparison of mental disorders with the patient's social status showed no correlation between the incidence of neuroses and social class the incidence of psychoses in the lowest classes was nearly twice that of the two highest classes and 50 per cent higher than in social class IV The incidence of schizophrenia increased evenly towards the low end of the grading Jaco (41) in 1960 correlated the incidence of diseases with occupational position He found the highest incidence of psychoses and schizophrenia among the unemployed the professionals and the semiprofessionals. As for education those with 1—4 years of formal schooling had the highest incidence Following this educational group came the one with an academic degree

A comparison between Hollingshead's and Jaco's results based on classification by both occupational position and education reveals a contradiction

Inghe (1959) pointed out the lack of agreement on mental disorders and the contradictory results on the importance of social factors A point worth making however is the relative agreement on oligophrenia being more common in the lower social classes Several studies of the relationship between the economic

sense of the word, are originally »classless«. In their own study however they came to the conclusion that the child's social background affected the treatment received in psychiatric disease. This same result was already reported by Hollingshead and Redlich (36): the character of psychiatric therapy was correlated with the patient's social standing.

Lowe (1966), from his study of schizophrenia in early childhood, found that the parents of these children were on a higher occupational level than those of children with other psychic disorders, and that the family of a schizophrenic child was not so often dissolved. Boys were affected with schizophrenia more than twice as often as girls, but the seniority among siblings was not linked with any distinct differences. The author also pointed out potential sources of error: for example, parents on a lower educational level do not notice the characteristic behaviour of a schizophrenic child, and therefore fail to seek medical advice. It is possible that these children are finally admitted with an indefinite diagnosis of mental retardation. In trying to trace the etiologic factors, Lowe pays attention to harmony in the family and underlines the coarseness of our yardstick when we measure e.g. divorces, while in reality we should measure the way in which the parents settle their mutual disagreement and the number of points on which they disagree.

Usually in children's diseases and especially in their psychic disorders, attention has been given to the part played by the mother. Mastropaolo (1967), from his study of juvenile delinquents, came to the conclusion that *the father's role in mental disorders* is highly significant. The father/son relationship, as the author demonstrates, is directly connected with the background of the disturbed behaviour of juvenile delinquents. An absent or weak father figure has a detrimental effect on the development of the son's character. In practice, the father's role is to set an example for the son and to teach correct behaviour patterns. If the father is unable to assume this role, or is otherwise out of balance, the result may be maladjustment of the son. The father should also be able to lead the normal antagonism which exists in boys in pre-puberty and puberty into their right channels, so that it would not be released by rebelling against the laws and accepted morals of the community.

Some authors have concentrated on certain aspects of the family crisis with a retarded child before institutionalization — in the situation where hospital admission is a possibility. Saenger (1960) found that persons committed to an institution for the retarded tended to have lower intelligence, were more likely to come from an ethnic minority, and had required more time and attention from family members than those who were not institutionalized. Behaviour problems, hyperactivity, aggression or sexual maladjustment were the most important factors leading to commitment. Farber (1959) found that willingness to place a retarded child in an institution was related in a complex way to the sex of the child, the social status and religion of the family, and the marital integration of the parents. Mercer (1967) pointed out in his study of patterns of family crisis related to reacceptance of the retarded that there are two crisis patterns: the burden-of-care crisis and the interpersonal structural stress crisis. All families are equally likely to report the latter, but families who leave their retardates in the institution are more likely to report the former.

Grad and Sainsbury (1966) discussed the difficulties a mentally ill family member causes at home and the chances of treating a mentally ill patient at home. Sending a mentally ill patient to hospital is a *difficult* problem for the family. There is no doubt that many families would prefer to keep the patient at home, even though there may be difficulties and excessive burdens of work. The authors restricted themselves completely to adult psychiatric cases. In the event of mentally ill children, the mother's feelings of guilt, mutual controversies inside the family, the parents' desire to protect the child and to counter their subconscious feelings of guilt and self-pity should also be taken into consideration.

developing psyche The author also devoted attention to the negative aspects of strictly dogmatic and narrow religious mind for the developing psyche A home which lays excessive emphasis on religion arousing fear in the children and making exaggerated demands on them damages the growing psyche and this damage is reflected in the need for psychic therapy

In Finland Frisk (1968) dealt with the numerous problems of teenagers Of these problems can be mentioned various psychiatric, psychosomatic and social disorders and behind them both psychophysical development and »circulus vitiosus» between this and neighbourhood

Tizard (1966) devoted attention to the important role of mental subnormality in child psychiatry and to the difficulty of distinguishing, especially in children between mental retardation and definite child psychiatric diseases The author also emphasized that no universally accepted classification of children s mental disorders is available Nor has the incidence of mental disorders among children been studied in detail any more than has the number of children requiring the help of child guidance clinics.

Eaton (1967) pointed out that most diagnoses of emotional disturbances in children can be made on an outpatient basis Hospitalization for diagnosis is, however preferable when the admitting physician may require factual reporting of symptomatic behaviour or want to determine whether the child will or can behave differently if offered opportunity in an accepting supporting relatively neutral environment He may also want to further evaluate and elaborate outpatient data when this information is inconclusive

Eaton also stressed that hospitalization for treatment is indicated when the child is dangerous to himself or others, or when his behaviour has become intolerable to his home or community It is also indicated when outpatient therapy is failing or when habit training at home has been unsuccessful and the parents are too involved in the negative cycle to handle the problem constructively themselves.

MacDermott and co-workers (1967) underlined the same diagnostic difficulty and lack of classification The writers said that there are no standard tests for mental disorders, the psychiatrist himself is the diagnostic instrument In their own study, on American children the authors were unable to show any statistically significant difference in childhood psychoses between the occupational groups. They came to the conclusion that the composition of the material was a result of selection and that the upper socio-economic groups had better medical facilities available and paid more attention to the abnormal behaviour of their children The upper classes can obtain private treatment for their children while the lower classes must consult community health resources Parents may prefer to have their psychotic children diagnosed and masked as mentally retarded since it is often easier to find special education for the retarded than for mentally diseased children The authors pointed out that children s maladjustment was based on acquired habits and behaviour inside the family

Miller et al (1960) stressed in their book that parents seldom consulted a physician for enuresis until the child was 5 years old The distribution of the cases of enuresis among the social classes revealed the most pronounced correlation between low social status and neglected physical care Matrimonial instability loss of one of the parents, and criminalism of the parents were most markedly correlated with enuresis

The authors also studied maladjustment of the child and found no statistically significant correlation to any environmental factor such as the stability of the family or poor social conditions Among the factors concerned with the child age was found to be of the greatest importance, in that maladjustment of long standing was most common among children over three years of age. Another personal factor was the sex the incidence among boys was twice as high as among girls.

Harrison et al (1965) built on the assumption that children in the social

sense of the word, are originally »classless» In their own study however they came to the conclusion that the child's social background affected the treatment received in psychiatric disease. This same result was already reported by Hollingshead and Redlich (36) the character of psychiatric therapy was correlated with the patient s social standing

Lowe (1966) from his study of schizophrenia in early childhood, found that the parents of these children were on a higher occupational level than those of children with other psychic disorders and that the family of a schizophrenic child was not so often dissolved Boys were affected with schizophrenia more than twice as often as girls, but the seniority among siblings was not linked with any distinct differences. The author also pointed out potential sources of error for example, parents on a lower educational level do not notice the characteristic behaviour of a schizophrenic child and therefore fail to seek medical advice. It is possible that these children are finally admitted with an indefinite diagnosis of mental retardation. In trying to trace the etiologic factors, Lowe pays attention to harmony in the family and underlines the coarseness of our yardstick when we measure e.g. divorces, while in reality we should measure the way in which the parents settle their mutual disagreement and the number of points on which they disagree.

Usually in children s diseases and especially in their psychic disorders, attention has been given to the part played by the mother *Mastropaolo* (1967) from his study of juvenile delinquents, came to the conclusion that the father s role in mental disorders is highly significant. The father/son relationship, as the author demonstrates, is directly connected with the background of the disturbed behaviour of juvenile delinquents An absent or weak father figure has a detrimental effect on the development of the son s character In practice, the father's role is to set an example for the son and to teach correct behaviour patterns. If the father is unable to assume this role, or is otherwise out of balance the result may be maladjustment of the son. The father should also be able to lead the normal antagonism which exists in boys in prepuberty and puberty into their right channels, so that it would not be released by rebelling against the laws andaccepted morals of the community

Some authors have concentrated on certain aspects of the family crisis with a retarded child before institutionalization — in the situation where hospital admission is a possibility Saenger (1960) found that persons committed to an institution for the retarded tended to have lower intelligence, were more likely to come from an ethnic minority and had required more time and attention from family members than those who were not institutionalized. Behaviour problems, hyperactivity aggression or sexual maladjustment were the most important factors leading to commitment. Farber (1959) found that willingness to place a retarded child in an institution was related in a complex way to the sex of the child, the social status and religion of the family and the marital integration of the parents. Mercer (1967) pointed out in his study of patterns of family crisis related to reacceptance of the retarded that there are two crisis patterns the burden-of care crisis and the interpersonal structural stress crisis All families are equally likely to report the latter but families who leave their retardates in the institution are more likely to report the former

Grad and Sainsbury (1966) discussed the difficulties a mentally ill family member causes at home and the chances of treating a mentally ill patient at home. Sending a mentally ill patient to hospital is a difficult problem for the family There is no doubt that many families would prefer to keep the patient at home, even though there may be difficulties and excessive burdens of work The authors restricted themselves completely to adult psychiatric cases. In the event of mentally ill children, the mother's feelings of guilt, mutual controversies inside the family the parents' desire to protect the child and to counter their subconscious feelings of guilt and self pity should also be taken into consideration.

developing psyche The author also devoted attention to the negative aspects of strictly dogmatic and narrow religious mind for the developing psyche. A home which lays excessive emphasis on religion arousing fear in the children and making exaggerated demands on them, damages the growing psyche and this damage is reflected in the need for psychic therapy

In Finland Frisk (1968) dealt with the numerous problems of teenagers Of these problems can be mentioned various psychiatric psychosomatic and social disorders and behind them both psychophysical development and »circulus vitiosus» between this and neighbourhood

Tizard (1966) devoted attention to the important role of mental subnormality in child psychiatry and to the difficulty of distinguishing, especially in children between mental retardation and definite child psychiatric diseases The author also emphasized that no universally accepted classification of children's mental disorders is available Nor has the incidence of mental disorders among children been studied in detail any more than has the number of children requiring the help of child guidance clinics

Eaton (1967) pointed out that most diagnoses of emotional disturbances in children can be made on an outpatient basis Hospitalization for diagnosis is, however preferable when the admitting physician may require factual reporting of symptomatic behaviour, or want to determine whether the child will or can behave differently if offered opportunity in an accepting supporting relatively neutral environment He may also want to further evaluate and elaborate outpatient data when this information is inconclusive.

Eaton also stressed that hospitalization for treatment is indicated when the child is dangerous to himself or others, or when his behaviour has become intolerable to his home or community It is also indicated when outpatient therapy is failing or when habit training at home has been unsuccessful and the parents are too involved in the negative cycle to handle the problem constructively themselves.

MacDermott and co-workers (1967) underlined the same diagnostic difficulty and lack of classification The writers said that there are no standard tests for mental disorders, the psychiatrist himself is the diagnostic instrument. In their own study on American children the authors were unable to show any statistically significant difference in childhood psychoses between the occupational groups. They came to the conclusion that the composition of the material was a result of selection and that the upper socio-economic groups had better medical facilities available and paid more attention to the abnormal behaviour of their children The upper classes can obtain private treatment for their children while the lower classes must consult community health resources. Parents may prefer to have their psychotic children diagnosed and masked as mentally retarded since it is often easier to find special education for the retarded than for mentally diseased children The authors pointed out that children's maladjustment was based on acquired habits and behaviour inside the family

Miller et al (1960) stressed in their book that parents seldom consulted a physician for enuresis until the child was 5 years old The distribution of the cases of enuresis among the social classes revealed the most pronounced correlation between low social status and neglected physical care Matrimonial instability loss of one of the parents and criminalism of the parents were most markedly correlated with enuresis

The authors also studied maladjustment of the child and found no statistically significant correlation to any environmental factor such as the stability of the family or poor social conditions. Among the factors concerned with the child, age was found to be of the greatest importance, in that maladjustment of long standing was most common among children over three years of age Another personal factor was the sex the incidence among boys was twice as high as among girls.

Harrison et al. (1965) built on the assumption that children in the social

Material and methods

As mentioned, the collecting of the data was carried out in 1962 by preparing a comprehensive questionnaire of 70 selected questions[1] (Appendix) to be completed in different hospitals simultaneously. Only two children's wards, Tampere Central Hospital in middle west Finland (66 beds) and a children's hospital (Åboland Sjukhus) in Turku (30 beds) which serves the archipelago on the southwest coast, could not participate for local reasons. All the other 21 children's departments in the country were included in the study (Fig. 1). The prospective method was used, having considerable advantages compared with the retrospective method in this type of data collection (44–46). A meeting of the head physicians of all participating 21 children's hospitals was held and more detailed instructions for the study were given.

The study was conducted in three phases: the first in April and May 1963, the second in August 1963 and third in January 1964, in order to reflect the mean situation of the year of investigation. The series consisted of a total of 7954 child patients, divided into three phases presented in Table 1. The total number of beds for children in the participating hospitals was 1462 and the total number of children treated in them in 1963 was 28,635. The present material covered 27.8 per cent.

MAP 1

GEOGRAPHICAL DISTRIBUTION OF PEDIATRIC UNITS IN FINLAND — TYPES 1-4 —

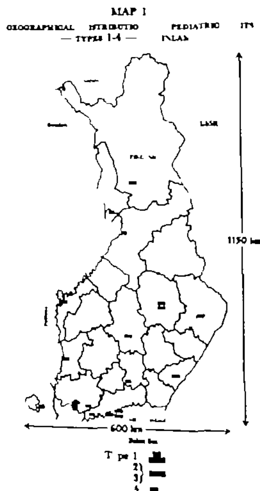


TABLE 1

DISTRIBUTION OF THE MATERIAL BY PERIODS OF THE STUDY

	Number of admissions	Per cent
First period	4521	56.8
Second period	999	12.6
Third period	2434	30.6
Total	7954	100.0

[1] by Niilo Hallman, M.D., Ole Wasz-Höckert, M.D. and Eero H. Valanne, M.D. with consultative assistance of Elina Haavio-Mannila, Dr.Pol.Sc.

Purpose of the study

I The first purpose of the present study was to find out the factors connected with child home and hospital which constituted the social or psychological indications influencing the hospital admission of children

II The second purpose was to elucidate socio-economic and socio-psychological background factors in the diagnosis groups of mental disorders and so called functional symptoms of children

Material and methods

As mentioned, the collecting of the data was carried out in 1962 by preparing a comprehensive questionnaire of 70 selected questions[1] (Appendix) to be completed in different hospitals simultaneously. Only two children's wards, Tampere Central Hospital in middle-west Finland (66 beds) and a children's hospital (Åboland Sjukhus) in Turku (30 beds) which serves the archipelago on the south west coast, could not participate for local reasons. All the other 21 childrens departments in the country were included in the study (Fig. 1). The prospective method was used, having considerable advantages compared with the retrospective method in this type of data collection (44–46). A meeting of the head physicians of all participating 21 children's hospitals was held and more detailed instructions for the study were given.

The study was conducted in three phases: the first in April and May 1963, the second in August 1963 and third in January 1964 in order to reflect the mean situation of the year of investigation. The series consisted of a total of 7954 child patients, divided into three phases presented in Table 1. The total number of beds for children in the participating hospitals was 1462 and the total number of children treated in them in 1963 was 28,635. The present material covered 27.8 per cent

MAP 1

GEOGRAPHICAL DISTRIBUTION OF PEDIATRIC UNITS — TYPES 1-4 — IN FINLAND

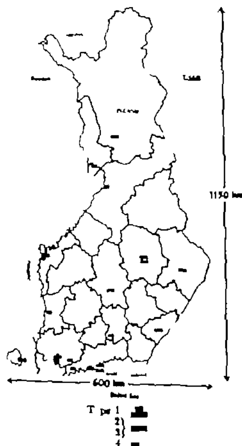


TABLE 1

DISTRIBUTION OF THE MATERIAL BY PERIODS OF THE STUDY

	Number of admissions	Per cent
First period	4521	56.8
Second period	999	12.6
Third period	2434	30.6
Total	7954	100.0

by Niilo Hallman, M.D., Ole Wasz-Höckert, M.D. and Eero H. Valanne, M.D. with consultative assistance of Elina Haavio-Mannila, Dr.Pol.Sc.

of all children admitted to hospital in Finland during the whole year (Table 2) The sample consequently represents a period of one year

Table 2 shows the distribution of the sample according to hospital and for comparison the same for all the children admitted during 1963 The percentages of completed questionnaires out of the total number of admissions are presented

The central hospitals treat some groups of children in wards other than the pediatric, such as child patients undergoing surgery or those with ophthalmic, otologic and dermatologic diseases The study only covered the patients of the pediatric wards, although e g Children s Hospital of the University of Helsinki and the City Hospital of Helsinki included pediatric surgical patients in their series.

Completing of the questionnaire

The first 39 questions dealing with socio-economic and socio-psychological factors in the family were completed by nurses and social workers or in teaching hospitals, by interns with the help of medical students in connection with the admission of the child The information was supplied in the majority of the cases by the mother who usually brought the child to hospital (Table 3)

The questions dealing with parents attitudes (Nos 40—44) were filled in by ward nurses when the child was dis

TABLE 2

BEDS AND ADMISSIONS OF CHILDREN IN THE PARTICIPATING HOSPITALS, AND THE NUMBER O ADMISSIONS IN THE PRESENT SERIES WITH PERCENTAGES VERSUS TOTAL ADMISSIONS TO RESPECTIVE HOSPITAL

Hospital	Beds for children 1963	Admissions in 1963	Present series: Number of admissions	Present series: Per cent	Present series: Per cent of all admissions in each hospital
1 Children s Hosp tal, University of Helsinki	270	5968	1438	18.1	24 1
2 Children s Hospital, U iversity of Turku	70	1807	450	5.7	24 9
3 Children s Castle, Helsinki	200	1330	376	4 7	28.3
4 City Hospital of Helsinki (Aurora)	166	2663	1232	15.5	46 3
5 Lapland Children s Hospital, Rovaniemi	110	2388	796	10.0	33 3
6 Savo Children s Castle, Kuopio	80	1016	326	4 1	32 1
7 North Carelia Central Hospital Joensuu	56	674	292	3 7	43.3
8. South Saimaa Central Hospital, Lappeenranta	47	1433	416	5.6	31 1
9 Central Finland Central Hospital, Jyväskylä	41	1833	462	5 8	25 2
10 Central Hospital, Kuopi	44	1293	174	2 2	13 5
11 Central Hospital, Vaasa	38	850	241	3 0	28.4
12 Central Hospital, Savonlinna	25	594	140	1 8	23.6
13 Central Hospital, Kemi	25	738	113	1 4	15.3
14 City Hospital for Infectious Diseases, Turk	68	861	264	3 3	30 7
15. Provincial Hospital, Mikkeli	49	1108	253	3 2	22 8
16. City Hospital Lahti	38	792	252	3 2	31.8
17 Provincial Hospital, Oulu	37	888	278	3 5	31 3
18. Provincial Hospital Hämeenlinna	28	686	44	0.6	6.4
19 Provincial Hospital, Pori	27	755	175	2.2	23 2
20. District Hospital, Salo	15	608	128	1 6	21 1
21 Provincial Hospital Tammisaari	15	195	51	0.6	26.2
	1452	28635	7931	100.0	27.8

TABLE 3

PERCENTAGE DISTRIBUTION OF THE MATERIAL BY SOURCE OF INFORMATION, OR THE PERSON WHO BROUGHT THE CHILD TO HOSPITAL

	Per cent
Mother	72.0
Father	12.4
Both parents	8.4
Non-relative person	2.4
Other relative	1.8
Child personally	1.0
Not known	2.0
	100.0

charged from the hospital. The nurses had several opportunities to make observations on the parent's attitudes e.g during visiting hours.

The last six items dealing with diagnosis and some hospital factors were completed by the physician in charge of the ward when the patient was discharged. The physician made his judgement for each case as a whole taking into consideration the whole hospitalization period

By final diagnosis was meant the disease which resulted in hospital admission The final diagnosis was a conclusion reached in the ward The admission diagnosis could be only tentative.

In the present material the classification by diagnosis was made using the final diagnosis. Four-digit figures of the international nomenclature of diseases (WHO 1948) were used as the diagnosis numbers in the questionnaire[1]

Because of lack of other generally accepted nomenclature the WHO nomenclature was used but it may be incomplete and is only symptomatic not etiological.

Although the distribution tables carry the official WHO nomenclature used in the present study to make comparisons with official statistics from both here and abroad possible, other classifications of diagnoses (especially in child psychiatry) such as diagnosis by etiology or by severity or grade of the disorder would actually convey more.

Distribution of the material by indications for admission based on hospital physician's opinion is seen in Table 4

TABLE 4

DISTRIBUTION OF THE PRESENT SERIES BY INDICATION FOR ADMISSION

	Number of admissions	Per cent
Purely medical indications	7159	90.8
Partly or decisively social reasons	552	7.0
Psychological factors in the family	176	2.2
Total	7890	100.0
Indication unknown	64	
All together	79.4	

Social and psychological factors

In the present study *social factors* influencing the admission of children to hospital were those additional factors preventing adequate home care and the result of difficult socio-economic back-ground

The *psychological mechanisms* in the hospital admission of children might consist of following factors (79)

- the parental psychological tolerance limit
- the readiness of the referring physician to pass the child on
- the physician's own burden of work
- his lack of examination facilities
- his lack of familiarity with pediatrics
- his readiness to be influenced by the social and psychological factors in the family of the child
- the hospital physic

[1] As known the WHO nomenclature was modernized and renewed in 1968.

2

of all children admitted to hospital in Finland during the whole year (Table 2). The sample consequently represents a period of one year.

Table 2 shows the distribution of the sample according to hospital and for comparison, the same for all the children admitted during 1963. The percentages of completed questionnaires out of the total number of admissions are presented.

The central hospitals treat some groups of children in wards other than the pediatric, such as child patients undergoing surgery or those with ophthalmic, otologic and dermatologic diseases. The study only covered the patients of the pediatric wards although e.g. Children's Hospital of the University of Helsinki and the City Hospital of Helsinki included pediatric surgical patients in their series.

Completing of the questionnaire

The first 39 questions dealing with socio-economic and socio-psychological factors in the family were completed by nurses and social workers or in teaching hospitals, by interns with the help of medical students in connection with the admission of the child. The information was supplied in the majority of the cases by the mother who usually brought the child to hospital (Table 3).

The questions dealing with parents' attitudes (Nos 40—44) were filled in by ward nurses when the child was dis-

TABLE 2

BEDS AND ADMISSIONS OF CHILDREN IN THE PARTICIPATING HOSPITALS, AND THE NUMBER OF ADMISSIONS IN THE PRESENT SERIES WITH PERCENTAGES VERSUS TOTAL ADMISSIONS TO RESPECTIVE HOSPITAL

Hospital	Beds for children 1963	Admissions in 1963	Present series: Number of admissions	Present series: Per cent	Present series: Per cent of all admissions in each hospital
1 Children's Hospital, University of Helsinki	270	5968	1438	18.1	24.1
2. Children's Hospital, University of Turku	70	1807	450	5.7	24.9
3 Children's Castle, Helsinki	200	1330	376	4.7	28.3
4 City Hospital of Helsinki (Aurora)	166	2663	1232	15.5	46.3
5. Lapland Children's Hospital, Rovaniemi	110	2388	796	10.0	33.3
6 Savo Children's Castle, Kuopio	80	1016	326	4.1	32.1
7 North Carelia Central Hospital, Joensuu	56	674	292	3.7	43.3
8. South Saimaa Central Hospital, Lappeenranta	47	1433	446	5.6	31.1
9 Central Finland Central Hospital, Jyvaskyla	44	1833	462	5.8	25.2
10 Central Hospital, Kuopio	44	1293	174	2.2	13.5
11 Central Hospital, Vaasa	38	850	241	3.0	28.4
12. Central Hospital, Savonlinna	25	594	140	1.8	[illegible]3.6
13. Central Hospital, Kemi	25	738	113	1.4	15.3
14. City Hospital for Infectious Diseases, Turku	68	861	264	3.3	30.7
15 Provincial Hospital, Mikkeli	49	1108	253	3.2	22.8
16. City Hospital, Lahti	38	792	252	3.2	31.8
17 Provincial Hospital, Oulu	37	888	278	3.5	31.3
18. Provincial Hospital, Hameenlinna	28	686	44	0.6	6.4
19 Provincial Hospital, Pori	27	755	175	2.2	23.2
20 District Hospital, Salo	15	608	128	1.6	21.1
21 Provincial Hospital, Tammisaari	1	195	51	0.6	26.2
	1432	28635	7931	100.0	27.8

Mental disorders constituted the first group (Table 6). The second group, functional symptoms reflected the group where the admission took place without any other diagnosis than symptomatic. Diagnoses such as e.g. icterus, hepatomegalia, dehydration and albuminuria, which indicated organic disorder without etiologic diagnosis, were excluded. The third group included all other admitted patients.

As pointed out by MacKeith (1961) it is difficult in childhood to distinguish between the somatic diseases, the mental disorders and the diseases which may be termed psychosomatic, and to demonstrate that psyche is a background factor contributing to the manifestation of a disease. It could be presumed that a psychologically unfavourable environment (quarrelsome family life, economic difficulties, frequent illness at home) may be one of the factors contributing to the outbreak of illness in a child. In this case, it could be assumed that the manifestation and symptoms would be hard to diagnose in specific terms. Recurrent attacks of abdominal pain, constipation, encopresis, enuresis, certain forms of asthma, headache are examples of childhood diseases customarily referred to this group.

On the basis of the foregoing, the functional symptoms group of the present series (Table 7) can perhaps be taken to reflect psychosomatic diseases to a cer-

TABLE 6

DISTRIBUTION OF THE MENTAL DISORDERS GROUP

Diagnosis (International nomenclature of diseases Nos. 300—326)	Number	Per cent
Habitus abnormis infantum	58	21.9
Oligophrenia alia	43	16.2
Maladaptatio acuta	27	10.2
Enuresis, personitas immatura indicans	20	7.5
Instabilitas emotionalis	15	5.6
Reactio hysterica, reactio angoris nondefinita	12	4.5
Deficientia intelligentiae	11	4.2
Dyslexia, dysphasia primaria	11	4.2
Reactio angoris	10	3.8
Mongolismus	8	3.0
Idiotia	8	3.0
Dystonia neurocirculatoria	7	2.6
Debilitas	6	2.3
Schizophrenia latens, psychosis schizoaffectiva	5	1.9
Psychosis non definita	3	1.1
Psychoneuroses aliae non definitae	3	1.1
Reactio hypochondrica	2	0.8
Reactio phobica	2	0.8
Others	14	5.3
Total series	265	100.0

TABLE 7

DISTRIBUTION OF THE FUNCTIONAL SYMPTOMS GROUP

Diagnosis (International nomenclature of diseases Nos. 780—783.0, 783.5—6, 786.9 and 790—795.5)	Number	Per cent
Observationes et explorationes casus definitae alii	195	33.2
Convulsiones non definitae	113	19.2
Colica non definita, dolores abdominalis nondef.	102	17.3
Observationes et explorationes casus non definitae	47	8.0
Cephalalgia non definita	16	2.7
Incontinentia alvi	14	2.4
Observationes et explorationes casus mentalis	14	2.4
Nausea, emesis	13	2.2
Motus abnormis involuntarius	12	2.0
Encephalopathia non definita	5	0.9
Laesio somni	5	0.9
Incontinentia urinae non definita	5	0.9
Anorexia non definita	4	0.7
Other neurological symptoms	17	2.9
Others	26	4.5
Total series	588	100.0

ician's decision for admission
- — availability of beds in the hospital
- — children coming without reference with an unknown background, whom he dares not send home
- — the reference suggests a serious diagnosis which must be verified or excluded
- — readiness to be influenced by the social and psychological background

All these factors were summarized as »psychological factors» in the present study

The physician's replies to the questions probably also reflected to some degree the prevailing attitudes among the pediatricians of Finland and their understanding of the social and psychological background of their patients

In considering the samples with respect *to freedom from bias the part played by* the fact that the estimates of parental attitudes were based on the subjective appraisal of the nurses must be borne in mind

Finnish nurses are trained in psychology and the ward nurses who completed the questionnaire on the child's discharge from hospital have a lot of experience of the hospital milieu and human behaviour

The fact that the study was carried out in twenty-one hospitals and numerous wards tends to counterbalance distortion in the appraisals (e.g too subjective or tinged by the observer's own psychic difference) of an individual nurse There were of course nurses who owing to their other obligations had no time to devote to an accurate assessment of each family and fathers whom the nurses never saw at all. But even the fact that the father did not pay a single visit to his child in the hospital may reflect *his attitude to* the child

Hospital nurses do tours of duty It is possible that some of the ward nurses completing the form did not happen to be on duty when the parents visited their child Visiting hours in 1963—64 in *Finnish hospitals* were restricted and relatively *short* one to three hours.

Classifications of some background factors

The *hospitals* were divided as follows, primarily according to their working facilities and operation (Fig 1 and Table 2)

1 University teaching hospitals (Helsinki and Turku) and a special hospital treating patients from the whole country (The Children's Castle in Helsinki)[1]

2 City Hospital of Helsinki (Aurora) whose patients were from a narrow limited metropolitan area, with some half a million of inhabitants.

3 Pediatric units with two or more pediatricians.

4 Pediatric units with one pediatrician only

Four sets of hospital factors were selected for closer studies hospital resources in different geographical parts of the country type of hospital waiting time for admission *and those factors which delayed the* discharge of patients

Classification by diagnosis The patients were divided into three major groups according to the final diagnosis (Table 5)

TABLE 5

DISTRIBUTION OF THE PRESENT SERIES INTO GROUPS ACCORDING TO THE FINAL DIAGNOSIS

Diagnostic groups and numbers[2]	Number of diagnoses	Per cent
Mental disorders		
Nos. 300—326	265	3.3
Functional symptoms		
Nos. 780—785.0, 785.5—6		
786.9 and 790—795.5	588	7 4
Other diseases	7101	89 3
Total	7954	100 0

[1] This pediatric medical center treats especially three groups of diseases cerebral palsy mental disorders and premature infants. (Professor Arvo Ylppo, M.D., was head of the hospital at that time)

[2] Numbers according to th international WHO nomenclature of diseases (1948)

Mental disorders constituted the first group (Table 6) The second group, functional symptoms, reflected the group where the admission took place without any other diagnosis than symptomatic. Diagnoses such as e.g icterus, hepatomegalia, dehydration and albuminuria, which indicated organic disorder without etiologic diagnosis, were excluded. The third group included all other admitted patients.

As pointed out by MacKeith (1961) it is difficult in childhood to distinguish between the somatic diseases, the mental disorders and the diseases which may be termed psychosomatic, and to demonstrate that psyche is a background factor contributing to the manifestation of a disease. It could be presumed that a psychologically unfavourable environment (quarrelsome family life, economic difficulties, frequent illness at home) may be one of the factors contributing to the outbreak of illness in a child in this case, it could be assumed that the manifestation and symptoms would be hard to diagnose in specific terms. Recurrent attacks of abdominal pain, constipation, encopresis, enuresis, certain forms of asthma, headache are examples of childhood diseases customarily referred to this group

On the basis of the foregoing, the functional symptoms group of the present series (Table 7) can perhaps be taken to reflect psychosomatic diseases to a cer

TABLE 6

DISTRIBUTIO THE MENTAL DISORDERS GROUP

Diagnosis (International nomenclature of diseases Nos. 300—326)	Number	Per cent
Habitus abnormis infantum	58	21.9
Oligophrenias aliae	43	16.2
Maladaptatio acuta	27	10.2
Enuresis, personam immaturam indicans	20	7.5
Instabilitas emotionalis	15	5.6
Reactio hysterica, reactio angoris nondefinita	12	4.5
Deficientia intelligentiae	11	4.2
Dyslexia, dysphasia primaria	11	4.2
Reactio angoris	10	3.8
Mongolismus	8	3.0
Idiotia	8	3.0
Dystonia neurocirculatoria	7	2.6
Debilitas	6	2.3
Schizophrenia latens, psychosis schizoaffectiva	5	1.9
Psychosis non definita	3	1.1
Psychoneuroses aliae non definitae	3	1.1
Reactio hypochondrica	2	0.8
Reactio phobica	2	0.8
Others	14	5.3
Total series	265	100.0

TABLE 7

DISTRIBUTION THE FUNCTIONAL SYMPTOMS GROUP

Diagnosis (International nomenclature of diseases Nos. 780—785.0, 785.5—6, 786.9 and 790—795.5)	Number	Per cent
Observationes et explorationes casus definitae alii	195	33.2
Convulsiones non definitae	113	19.2
Colica non definita, dolores abdominis nondef.	102	17.3
Observationes et explorationes casus non definitae	47	8.0
Cephalalgia non definita	16	2.7
Incontinentia alvi	14	2.4
Observationes et explorationes casus mentalis	14	2.4
Nausea, emesis	13	2.2
Motus abnormis involuntarius	12	2.0
Encephalopathia non definita	5	0.9
Laesio somni	5	0.9
Incontinentia urinae non definita	5	0.9
Anorexia non definita	4	0.7
Other neurological symptoms	17	2.9
Others	26	4.3
Total series	588	100.0

tain extent. The group also measures the parental desire to have their child examined for symptoms on the basis of which the physician failed to give a specific diagnosis The group thus indicates also the cases in which the physician encountered the greatest diagnostic difficulties

»Convulsiones non definitae» covered mainly fever and affect cramps, generally cramps in which no definite disease could be found and were included in the group of functional symptoms Neurologicaly verified epilepsy was graded elsewhere Some hospitals may of course have given this symptomatic number to conditions which were dubiously epileptiform cramps but most indefinite cramps in the present series did obviously not represent epilepsy

Classification by socio-economic factors The material was divided according to some factors, in order to estimate the influence of social status or hospitalization

The variables selected were parental income the father's occupational position educational level and marital status number of inhabitants per room type of child s domicile and distances from home to the nearest physician and hospital An attempt was made to study the mutual correlations of some recorded factors

Such factors as mother s health mother s employment outside home ownership of a private car a TV set or a summer house were not classified as purely socio-economic factors but were considered more as socio-psychological factors

Parents readiness to seek admission to hospital for their child was studied by means of the following variables admission delay for economic reasons, did the parents seek medical advice in time, had the child been neglected at home, had the child been hospitalized previously for the same disease, had the mother father or any of the siblings been admitted to hospital

TV-ownership and socio-economic level of the family

To see how TV ownership correlated with the general socio-economic level of the family correlation analysis of certain variables associated with the concept of »socio-economic level» was carried out to throw light on the concept. The variables used for the farming population were the following

1 ownership of television
2 disposable living space (number of rooms per inhabitant)
3 cultivated field area

For non farmers the variables were

1 ownership of television
2 disposable living space
3 income level
4 father s educational level

For both population groups, the variables were dichotomized and correlated mutually (phi-coefficient)

Table 8 shows that for the farming population the area of field under plough definitely measures a different concept from that measured by TV-ownership and disposable living space which showed a moderate degree of mutual correlation (.59) and were apparently associated with the status concept Among non farmers the correlation was highest between income level and father s educational level (47) which were clearly associated with the concept of socio-economic status, but perhaps with urbanization also It may be pointed out that the ownership of TV which was considered a variable associated with enlightenment hardly correlated at all with the father s educational level among non farmers.

TABLE 8

INTERCORRELATIONS OF SOCIO-ECONOMIC STATUS VARIABLES

Farmers

	1	2
2	59	
3	08	09

Non-farmers

	1	2	4
	13		
4	22	11	
5	07	10	42

Intercorrelation of some other variables

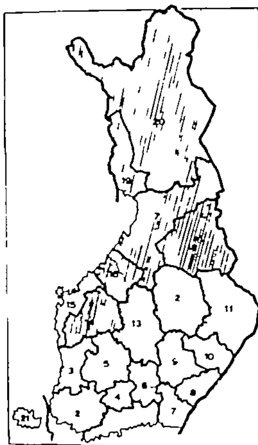
The intercorrelation of father's occupational status and parental income was also calculated. The phi-coefficient was 0.394 The intercorrelation was also determined between car ownership and parental income. It was 0.284 Cross-tabulation of summer cottage ownership and parental income showed an intercorrelation of 0.214 All this showed that the intercorrelation between father s occupational status, car ownership and summer cottage ownership was not very strong

Geographical distribution In an effort to study whether hospital conditions and general medical facilities were of importance in children s admission to hospital, it was found best to divide the geographical territory covered by the present study into two parts as widely different from each other as possible in community health resources.

Some central hospital districts of north and east Finland are in a poorer position than southern districts (26 74 103 104 106) The factors selected to measure the health resources of the region were the density of physician per 10 000 density of hospital beds per 1000 head of population and hospital visits of children per 1000 head of population (Table 9) The division is shown in Fig 2. The territory with poorer community health resources was called North Finland and the better equipped territory South Finland for the purposes of this study

MAP 2

GEOGRAPHICAL DISTRIBUTIO BY CENTRAL HOSPITAL DITRICTS INTO NORTH AN SOUTH INLAND



Shaded area = North Finland
White area = South F nland

Classification by the type of community The distribution by type of community can be made on various grounds. The material can be divided into an urban and rural population. However urban communities were divided into Helsinki and other towns, since Helsinki, a small

TABLE 9

RALATIV UMBER PHYSICIANS, HOSPITAL BEDS AND HOSPITAL VISITS OF CHILDREN IN NORTH SOUTH FINLAN (94 106)

	Physicians per 10 000 inhabitants in 1963	Hospital beds per 1000 inhabitants in 1963	Hospital visits of children per 1000 inhabitants in 1960
North Finland	3.7	3.6	54.2
South Finland	6.7	4.4	51.1

metropolis, represented a special type of urban settlement and had in addition the best health resources in Finland. The rural areas were divided into urbanized districts (= market boroughs) and rural districts proper. The latter division did not perhaps reflect very distinct differences as the difference between some industrialized rural centres and small urban districts may be narrow (4).

Statistical techniques

The statistical test applied was the chi square test for fourfold table, with Yates' correction for continuity. The fourfold tables were formed by cross-tabulation of, for instance, psychological/other admissions and legitimacy/illegitimacy. A respective test was carried out for the social admissions (social/other admissions vs. legitimacy/illegitimacy). In some cases, several classes were combined into one for testing; this is indicated in the tables.

Three levels of significance were used:

– highly significant ($p \leq 0.001$)
– significant ($0.001 < p \leq 0.01$)
– almost significant ($0.01 < p \leq 0.05$)

The asterisks corresponding to one test appear after two percentage figures, namely the percentages of indication (or disease) type in both classes of the background factor in question.

The phi coefficient of correlation (McNemar 1955, pp. 202—203) was applied in measuring the degree of co-variation between dichotomized socio-economic status variables.

The data were processed in the Computer Center of University of Oulu with an Elliott 803 computer.

As was shown e.g. by Feldstein and Butler (1965) in their paper, the study of an individual social factor or the study of several factors separately does not provide the correct picture of the mutual relations. Many factors are more or less interdependent. In order to reach a result as close to reality as possible, the mutual relations of the factors must be taken into account. This is best achieved using multivariate analysis.

In the present study, however, multivariate analysis was not used, mainly because of lack of sufficient experience about this type of studies. It must be borne in mind throughout, however, that the factors can be mutually interdependent.

Results

I

SOCIAL AND PSYCHOLOGICAL FACTORS IN THE HOSPITAL ADMISSION OF CHILDREN

Factors connected with the child

SEX

Of the child patients of the present series, 43.3 per cent were girls and 56.7 per cent boys.

A study of the group in which psychological indications affected admission to hospital reveals that the group consisted of 38.6 per cent girls and 61.4 per cent boys. In the social indications group the corresponding distribution was 41.4 per cent girls and 58.6 per cent boys.

A comparison of whether psychological or social indications affected the admission of boys more often than that of the girls revealed no significant differences.

When the percentages of the sexes in the age groups of the present study and in those of the total Finnish population are compared, the over representation of boys emerges distinctly (Table 10)

LEGITIMACY

4.3 per cent of the children of the present study were born out of wedlock, while 95.7 per cent were legitimate.

The frequency of psychological indications was not significantly different in legitimate and illegitimate children.

Social indications were more frequent for the illegitimate than the legitimate children. The difference was highly significant ($\chi^2 = 150.72$ $p < 0.001$) Table 11

TABLE 10

DISTRIBUTION OF THE MATERIAL BY SEX AND AGE COMPARED WITH TOTAL POPULATION OF CHILDREN IN FINLAND IN 1963 AND 1964

	Present study		All Finland 1963		All Finland 1964	
	N	%	N	%	N	%
Age group 0–1 years						
Girls	1113	42.8	39 551	48.9	38 687	48.9
Boys	1485	57.2**	41 364	51.1	40 446	51.1
Total	2598	100.0	80 915	100.0	79 133	100.0
Age group 2–6 years						
Girls	1415	42.7***	235 501	49.0	234 073	49.0
Boys	1898	57.3**	245 144	51.0	243 401	51.0
Total	3313	100.0	480 645	100.0	477 474	100.0
Age group 7–13 years						
Girls	831	45.4	399 896	49.1	390 929	49.0
Boys	999	54.6*	415 896	50.9	407 076	51.0
Total	1830	100.0	815 792	100.0	798 005	100.0

metropolis represented a special type of urban settlement and had in addition the best health resources in Finland The rural areas were divided into urbanized districts (= market boroughs) and rural districts proper The latter division did not perhaps reflect very distinct differences as the difference between some industrialized rural centres and small urban districts may be narrow (4)

Statistical techniques

Th statistical test pplied was the chi square test for fourfold table, with Yates correction for continuity The fourfold tables were formed by cross-tabulation of for instance, psychological/other admissions and legitimacy/illegitimacy A respective test was carried out for the social admissions (social/other admissions vs. legitimacy/illegitimacy) In some cases, several classes were combined into one for testing this is indicated n the tables.

Three levels of significance were used

- *** = highly significant ($p \leq 0.001$)
- ** = significant ($0.001 < p \leq 0.01$)
- * = almost significant ($0.01 < p \leq 0.05$)

The asterisks corresponding to one test appear after two percentage figures, namely the percentages of indication (or disease) type in both classes of the background factor in question.

The phi coefficient of correlation (McNemar 1955, pp. 202—203) was pplied in measuring the degree of co-variation between dichotomized socio-economic status variables.

The data were processed in th Computer Center of University of Oulu with an Elliott 803 computer

As was shown e.g by Feldstein and Butler (1965) in their paper the study of an individual social factor or the study of several factors separately does not provide the correct picture of the mutual relations. Many factors are more or less interdependent. I order to reach a result as close to reality as possible, the mutual relations of the factors must be taken into ccount. This is best achieved using multivariate analysis.

In the present study however multivariate analysis was not used, mainly because of lack of sufficient experience about this type of studies. It must be borne in mind throughout, however that the factors can be mutually interdependent.

SENIORITY AMONG SIBLINGS

The only child of the family was in question in 25.9 per cent of the admissions. 14.1 per cent were eldest children.

Tests were carried out in two sets first, only child versus others and second eldest child versus others

In psychological indications, no significant difference existed in the case of the only child or the eldest child in other words, psychological factors did not affect the admission of the only or the eldest child any more often than they affected that of the other children.

Social indications affected the child's admission more often when the only child was involved than when the child was one of several siblings. The difference was highly significant ($\chi^2 = 21.50$ $p < 0.001$) Table 12.

Factors connected with home and family

MOTHER'S EMPLOYMENT

35.1 per cent of the mothers of the children in the present study were employed outside the home 30.2 per cent worked full-time and 4.9 per cent were employed part-time.

A comparison of the frequencies of psychological and social indications for hospital admission between the mothers employed outside home and those staying at home revealed no significant differences.

When the full time employed mothers were tested against all others there were more social indications in the full time working group than in the others. The difference was highly significant ($\chi^2 = 149.0$ $p < 0.001$) Table 13

MOTHER'S STATE OF HEALTH

92.5 per cent of the children had a healthy mother while 7.5 per cent had a sick mother or a mother in poor physical condition

The frequency of psychological factors did not differ between the healthy and the sick or physically poor-condition mothers.

Additional social factors contributed to hospital admission more often when the mother was sick or in poor physical condition than when she was healthy The difference was highly significant ($\chi^2 = 26.92$ $p < 0.001$) Table 14

INCOME OF PARENTS

40.2 per cent of the parents in the present series were in the income bracket below 600 mk/month 15.6 per cent of the parents made more than 1000 mk/month and 13.7 per cent were farmers.[1]

TABLE 14

DECISIONS FOR CHILD ADMISSION TO HOSPITAL ACCORDING TO MOTHER'S STATE OF HEALTH

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Healthy	159	(2.3 %)	427	(6.3 %)	6180	(91.4 %)	6766	(100 %)
Poor condition	9	(2.4 %)	42	(11.4 %) ***	319	(86.2 %)	370	(100 %)
Sick	4	(2.2 %)	25	(13.9 %)	151	(83.9 %)	180	(100 %)
Total	172	(2.4 %)	494	(6.8 %)	6650	(90.8 %)	7316	(100 %)
					Not reported		638	
							7954	
					Non-response rate		8.0 %	

[1] 600 Fmk was at that time (1963—64) equivalent to 186 U.S. $ and 1000 Fmk to 310 U.S. $.

TABLE 11

INDICATIONS OR CHILD'S ADMISSION TO HOSPITAL BY LEGITIMACY OR ILLEGITIMACY

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Legitimate children	170	(2.4 %)	442	(6.2)	6503	(91.4 %)	7115	(100 %)
Illegitimate children	6	(1.9 %)	77	(24.4 %)	233	(73.7)	316	(100 %)
Total	176	(2.4)	519	(7.0)	6736	(90.6 %)	7431	(100 %)
					Not reported		523	
							7954	
					Non-response rate		6.6 %	

TABLE 12

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY ITS SENIORITY AMONG SIBLINGS

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
No siblings	4	(2.3)	183	(9.3)	1742	(88.4)	1970	(100)
Eldest	4	(2.2 %)	58	(5.4)	987	(92.4)	1069	(100)
2nd or 3rd child	80	(2.5 %)	209	(6.6)	2875	(90.9 %)	3164	(100)
4th or 5th child	28	(3.0)	53	(5.6)	863	(91.4)	944	(100)
6th to 16th child	2	(0.4)	27	(6.0 %)	424	(93.6 %)	453	(100)
Total	179	(2.4)	530	(7.0 %)	6891	(90.6 %)	7600	(100)
					Not reported		354	
							7954	
					Non-response rate		4.5	

TABLE 13

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY MOTHER'S EMPLOYMENT OUTSIDE THE HOME

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
No gainful employment	107	(2.3)	198	(4.2)	4358	(93.5)	4663	(100)
Part time employment	9	(2.6)	17	(4.9 %)	324	(92.5)	350	(100)
Full-time employment	55	(2.5 %)	275	(12.7 %)	1841	(84.8)	2171	(100 %)
Total	171	(2.4)	490	(6.8 %)	6255		7184	
					Not reported		770	
							7954	
					Non-response rate		9.7 %	

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents or foster parents of the child patients of the present study had a private car of their own.

Psychological factors affected the child's admission to hospital more often in those cases in which the family had a car of their own than in those in which the family had no car. The difference was significant ($\chi^2 = 9.41$, $p < 0.01$).

Additional social indications affected the admission more often if the family had no car. The difference was highly significant ($\chi^2 = 51.40$, $p < 0.001$). Table 16.

OWNERSHIP OF A TV SET

42.3 per cent of the homes of the child patients in the present study had a TV set.

Psychological factors affected the child's admission to hospital more often when the family had a TV set than when there was no TV. The difference was highly significant ($\chi^2 = 16.83$, $p < 0.001$).

No significant difference existed in social indications between the TV owners and those with no TV. Table 17.

TYPE OF COMMUNE

Of the children of the present study, 22.3 per cent came from Helsinki and 28.7 per cent from other towns, making a total of 51.0 per cent for urban children. 6.6 per cent came from market boroughs and 42.2 per cent from typical rural districts. If the market boroughs are classified as rural district, 49.0 per cent of the children came from communes of rural type.

A comparison of the urban and rural children revealed that psychological factors affected the admission of urban children slightly more often than that of the rural children. The difference was almost significant ($\chi^2 = 5.31$, $p < 0.05$).

Social indications were also more frequent for the urban than for the rural children. The difference was highly significant ($\chi^2 = 91.66$, $p < 0.001$).

A comparison of the Helsinki children with all others (the other towns, market boroughs and the rural districts) revealed no significant difference in the frequency of the psychological indications, whereas additional social indications were more frequent for the Helsinki children than for those from other localities. The difference was highly significant ($\chi^2 = 14.58$, $p < 0.001$). Helsinki did not differ significantly from the other towns, whereas a significant difference emerged between towns and rural areas. Table 18.

Factors connected with hospital

SOUTH AND NORTH FINLAND

77.4 per cent of the children of the present study came from South Finland and 22.6 per cent from North Finland

TABLE 17

INDICATIONS FOR CHILDS' ADMISSION TO HOSPITAL BY THE OWNERSHIP OF A TV SET AT HOME

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Television +	99	(3.3 %)**	190	(6.3 %)	2739	(90.4 %)	3028	(100 %)
Television −	72	(1.7 %)*	303	(7.3 %)	3757	(91.0 %)	4132	(100 %)
Total	171	(2.4 %)	493	(6.9 %)	6496	(90.7 %)	7160	(100 %)
					Not reported		794	
							7954	
					Non-response rate		10.0 %	

TABLE 15

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY AGGREGATE EARNINGS OF THE PARENTS

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
≤600 mk/month	47	(1 7 %)	273	(9 7 %)	2485	(88.6 %)	2805	(100 %)
600—1000 mk/month	47	(2.2 %)	126	(5.9 %)	1955	(91 9 %)	2128	(100 %)
>1000 mk/month	50	(4 6 %)	48	(4 4 %)	985	(91 0 %)	1083	(100 %)
Farmer family	24	(2 5 %)	28	(2 9 %)	903	(94 6 %)	955	(100 %)
Total	168	(2.4 %)	475	(6.8 %)	6328	(90.8 %)	6971	(100 %)
					Not reported		983	
							7954	
					Non-response rate		12.2 %	

Significance tests were carried out in three stages 1 farmers vs nonfarmers 2 < 600 mk/month vs. > 600 mk/month farmers excluded 3 600—1000 mk/month vs < 1000 mk/month farmers excluded

Frequencies of psychological factors did not differ significantly between farmers and non-farmers. Social indications affected the admission of farmers children less frequently than that of non farmers children The difference was highly significant ($\chi^2 = 25.56$ $p < 0.001$)

In the income bracket of a maximum 600 mk/month psychological factors affected admission to hospital less frequently than in the income bracket of over 600 mk/month The difference was highly significant ($\chi^2 = 11.03$ $p < 0.001$)

If parental income did not exceed 600 mk/month social indications affected admission more often than if the income exceeded 600 mk/month The difference was highly significant ($\chi^2 = 39.88$ $p < 0.001$)

When the income brackets were classified as a maximum of 1000 mk/month and over 1000 mk/month, psychological factors affected admission to hospital in the higher income bracket more often than in the lower The difference was highly significant ($\chi^2 = 17.53$ $p < 0.001$) Social indications affected the admission in the lower income bracket (maximum 1000 mk/month) more often than in the higher The difference was highly significant ($\chi^2 = 42.48$ $p < 0.001$) Table 15

TABLE 16

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY THE OWNERSHIP OF A PRIVATE CAR

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Private car +	73	(3.2 %)	82	(3.6 %)	2094	(93.2 %)	2249	(100 %)
Private car —	98	(2 0 %)	403	(8.3 %)	4362	(89 7 %)	4863	(100 %)
Total	171	(2 4 %)	485	(6.8 %)	6456	(90.8 %)	7112	(100 %)
					Not reported		842	
							7954	
					Non-response rate		10.6 %	

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents or foster parents of the child patients of the present study had a private car of their own.

Psychological factors affected the child's admission to hospital more often in those cases in which the family had a car of their own than in those in which the family had no car. The difference was significant ($\chi^2 = 9.41$, $p < 0.01$).

Additional social indications affected the admission more often if the family had no car. The difference was highly significant ($\chi^2 = 51.40$, $p < 0.001$). Table 16.

OWNERSHIP OF A TV SET

42.3 per cent of the homes of the child patients in the present study had a TV set.

Psychological factors affected the child's admission to hospital more often when the family had a TV set than when there was no TV. The difference was highly significant ($\chi^2 = 16.83$, $p < 0.001$).

No significant difference existed in social indications between the TV owners and those with no TV. Table 17.

TYPE OF COMMUNE

Of the children of the present study, 22.3 per cent came from Helsinki and 28.7 per cent from other towns, making a total of 51.0 per cent for urban children. 6.6 per cent came from market boroughs and 42.2 per cent from typical rural districts. If the market boroughs are classified as rural district, 49.0 per cent of the children came from communes of rural type.

A comparison of the urban and rural children revealed that psychological factors affected the admission of urban children slightly more often than that of the rural children. The difference was almost significant ($\chi^2 = 5.31$, $p < 0.05$).

Social indications were also more frequent for the urban than for the rural children. The difference was highly significant ($\chi^2 = 91.66$, $p < 0.001$).

A comparison of the Helsinki children with all others (the other towns, market boroughs and the rural districts) revealed no significant difference in the frequency of the psychological indications, whereas additional social indications were more frequent for the Helsinki children than for those from other localities. The difference was highly significant ($\chi^2 = 14.58$, $p < 0.001$). Helsinki did not differ significantly from the other towns, whereas a significant difference emerged between towns and rural areas. Table 18.

Factors connected with hospital

SOUTH AND NORTH FINLAND

77.4 per cent of the children of the present study came from South Finland and 22.6 per cent from North Finland.

TABLE 17

INDICATIONS FOR CHILD ADMISSION TO HOSPITAL BY THE OWNERSHIP OF A TV SET AT HOME

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Television +	99	(3.3 %)	190	(6.3 %)	2739	(90.4 %)	3028	(100 %)
Television —	72	(1.7 %)	303	(7.3 %)	3757	(91.0 %)	4132	(100 %)
Total	171	(2.4 %)	493	(6.9 %)	6496	(90.7 %)	7160	(100 %)
					Not reported		794	
							7954	
					Non-response rate		10.0 %	

TABLE 18

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF DOMICILE

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Helsinki	39	(2.3 %)	154	(9.1 %)	1502	(88.6 %)	1695	(100 %)
Other cities	68	(3.1 %)	223	(10.2 %)	1889	(86.7 %)	2180	(100 %)
Market boroughs	15	(3.0 %)	4	(4.8 %)	462	(92.2 %)	510	(100 %)
Rural communes	57	(1.8 %)	129	(4.0 %)	3038	(94.2 %)	3224	(100 %)
Total	179	(2.4 %)	530	(7.0 %)	6891	(90.6 %)	7600	(100 %)
					Not reported		354	
							7954	
					Non-response rate		4.4	

TABLE 19

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL IN SOUTH AND NORTH FINLAND

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
South Finland	147	(2.5 %)	469	(8.1 %)	5156	(89.4 %)	5772	(100 %)
North Finland	8	(1.7 %)	44	(2.6 %)	1610	(95.7 %)	1682	(100 %)
Total	175	(2.3 %)	513	(6.9 %)	6766	(90.8 %)	7454	(100 %)
					Not reported		500	
							7954	
					Non-response rate		6.3	

TABLE 20

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF HOSPITAL

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
University teaching hospitals and Children's Castle, Helsinki	86	(3.9 %)	105	(4.8 %)	2013	(91.3 %)	2204	(100 %)
City Hospital of Helsinki	2	(0.2 %)	117	(9.6 %)	1104	(90.2 %)	1223	(100 %)
Hospitals with several pediatricians	48	(2.0 %)	92	(3.8 %)	2309	(94.2 %)	2449	(100 %)
Hospitals with one pediatrician	43	(2.5 %)	216	(12.7 %)	1448	(84.8 %)	1707	(100 %)
Total	179	(2.4 %)	530	(7.0 %)	6874	(90.6 %)	7583	(100 %)
					Not reported		371	
							7954	
					Non-response rate		4.7 %	

Psychological factors were associated with hospital admission more often in the South than in the North. The difference was almost significant ($\chi^2 = 4.04$ $p < 0.05$)

The social indications also contributed to admission more often in South than in North Finland The difference was highly significant ($\chi^2 = 60.84$ $p < 0.001$) Table 19

TYPE OF HOSPITAL

29.1 per cent of the patients of the present study had been admitted to hospitals of Type 1 16.1 per cent to the City Hospital of Helsinki, 32.3 per cent to hospitals with several pediatricians and 22.5 per cent to hospitals with one pediatrician.

Significance tests have been carried out separately for every hospital type versus others.

Psychological indications were associated with admission to hospitals of Type 1 more often than with that to the other hospitals. The difference was highly significant ($\chi^2 = 31.10$, $p < 0.001$) In the City Hospital of Helsinki, psychological factors were associated less frequently than in the other hospital types. The difference was highly significant ($\chi^2 = 29.41$ $p < 0.001$)

Social indication affected admission to hospitals of Type 1 less often than that to the other hospitals. The difference w highly significant ($\chi^2 = 23.19$ $p < 0.001$) The admission to hospitals w th several pediatricians was also associated with social factors less frequently than that to the other hospitals. The difference was significant ($\chi^2 = 8.36$ $p < 0.01$) Admission to hospitals with one pediatrician was associated with social factors more often than that to the other hospitals. The difference was highly significant ($\chi = 107.60$ $p < 0.001$) The same was true of the City Hospital of Helsinki — that is to say social indications affected the admission more often than for the other types of hospitals. The difference was highly significant ($\chi^2 = 11.43$ $p < 0.001$) Table 20.

II

MENTAL DISORDERS AND FUNCTIONAL SYMPTOMS IN THE HOSPITAL ADMISSION OF CHILDREN

Indications for admission

When the effect of different factors on admissions for psychic diseases (= mental disorders) and for functional symptoms were compared, the first classification was purely medical vs. social and psychological indications. In the psychic diseases group, admissions for purely medical indications were fewer (2.5 per cent) than those for other indications (social indications 7.7 per cent and psychological indications 21.7 per cent) The difference was highly significant ($\chi^2 = 152.20$ $p < 0.001$) Admissions for functional symptoms were fewer on the basis of purely medical indications than medical combined with social and/or psychological contributory factors. The difference was highly significant ($\chi^2 = 13.77$ $p < 0.001$) Table 21

Factors connected with the child

SEX

56.6 per cent of the present series of children were boys and 43.4 per cent were girls. In the psychic diseases group 66.5 per cent were boys and 33.5 per cent girls. In the functional symptoms group 54.8 per cent were boys and 45.2 per cent girls.

A higher percentage of boys than girls was admitted to hospital for psychic diseases. The difference was significant ($\chi^2 = 10.54$ $p < 0.01$)

No significant difference between boys and girls was noted in the frequency of functional symptoms. Table 22.

AGE

12.0 per cent of the present series of children were less than 1 month old, 21.6 per cent 1—11 months, 42.3 per cent pre-school age (1—6 years) and 23.7 per cent school age (7—15 years)

For the statistical test the children were divided into two groups those up to

TABLE 18

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF DOMICILE

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
Helsinki	39	(2.5 %)	154	(9.1 %)	1502	(88.6 %)	1695	(100 %)
Other cities	68	(3.1 %)	223	(10.2 %)	1889	(86.7 %)	2180	(100 %)
Market boroughs	15	(3.0 %)	24	(4.8 %)	462	(92.2 %)	510	(100 %)
Rural communes	57	(1.8 %)	129	(4.0 %)	3038	(94.[illegible] %)	3224	(100 %)
Total	179	(2.4 %)	530	(7.0 %)	6891	(90.6 %)	7600	(100 %)
					Not reported		354	
							7954	
					Non-response rate		4.4	

TABLE 19

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL IN SOUTH AND NORTH FINLAND

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
South Finland	147	(2.5 %)	469	(8.1 %)	5156	(89.4 %)	5772	(100 %)
North Finland	28	(1.7 %)	44	(2.6 %)	1610	(95.7 %)	1682	(100 %)
Total	175	(2.3 %)	513	(6.9 %)	6766	(90.8 %)	7454	(100 %)
					Not reported		500	
							7954	
					Non-response rate		6.3 %	

TABLE 20

INDICATIONS FOR CHILD'S ADMISSION TO HOSPITAL BY TYPE OF HOSPITAL

	Psychological factors in the family		Social indications		Purely medical indications		Total series	
University teaching hospitals and Children's Castle Helsinki	86	(3.9 %)	105	(4.8 %)	2013	(91.3 %)	2204	(100 %)
City Hospital of Helsinki	2	(0.2 %)	117	(9.6 %)	1104	(90.2 %)	1223	(100 %)
Hospitals with several pediatricians	48	(2.0 %)	92	(3.8 %)	2309	(94.2 %)	2449	(100 %)
Hospitals with one pediatrician	43	(2.5 %)	216	(12.7 %)	1448	(84.8 %)	1707	(100 %)
Total	179	(2.4 %)	530	(7.0 %)	6874	(90.6 %)	7583	(100 %)
					Not reported		371	
							7954	
					Non-response rate		4.7	

Psychological factors were associated with hospital admission more often in the South than in the North. The difference was almost significant ($\chi^2 = 4.04$ $p < 0.05$)

The social indications also contributed to admission more often in *South than* in North Finland. The difference was highly significant ($\chi^2 = 60.84$ $p < 0.001$) Table 19

TYPE OF HOSPITAL

29.1 per cent of the patients of the present study had been admitted to hospitals of Type 1 16.1 per cent to the City Hospital of Helsinki, 32.3 per cent to hospitals with several pediatricians and 22.5 per cent to hospitals with one pediatrician.

Significance tests have been carried out separately for every hospital type versus others.

Psychological indications were associated with admission to hospitals of Type 1 more often than with that to the other hospitals. The difference was highly significant ($\chi^2 = 31.10$, $p < 0.001$) In the City Hospital of Helsinki psychological factors were associated less frequently than in the other hospital types. The difference was highly significant ($\chi^2 = 29.41$ $p < 0.001$)

Social indications affected admission to hospitals of Type 1 less often than that to the other hospitals. The difference was highly significant ($\chi^2 = 23.19$ $p < 0.001$) The admission to hospitals with several pediatricians was also associated with social factors less frequently than that to the other hospitals. The difference was significant ($\chi^2 = 8.36$ $p < 0.01$) Admission to hospitals with one pediatrician was associated with social factors more often than that to the other hospitals. The difference was highly significant ($\chi^2 = 107.60$ $p < 0.001$) The same was true of the City Hospital of Helsinki — that is to say social indications affected the admission more often than for the other types of hospitals. The difference was highly significant ($\chi^2 = 14.43$ $p < 0.001$) Table 20.

II

MENTAL DISORDERS AND FUNCTIONAL SYMPTOMS IN THE HOSPITAL ADMISSION OF CHILDREN

Indications for admission

When the effect of different factors on admissions for psychic diseases (= mental disorders) *and for functional symptoms* were compared, the first classification was purely medical vs. social and psychological indications. In the psychic diseases group admissions for purely medical indications were fewer (2.5 per cent) than those for other indications (social indications 7.7 per cent and psychological indications 21.7 per cent) The difference was highly significant ($\chi^2 = 152.20$, $p < 0.001$) Admissions for *functional* symptoms were fewer on the basis of purely medical indications than medical combined with social and/or psychological contributory factors. The difference was highly significant ($\chi^2 = 13.77$ $p < 0.001$) Table 21

Factors connected with the child

SEX

56.6 per cent of the present series of children were boys and 43.4 per cent were girls. In the psychic diseases group 66.5 per cent were boys and 33.5 per cent girls. In the functional symptoms group 54.8 per cent were boys and 45.2 per cent girls.

A higher percentage of boys than girls was admitted to hospital for psychic diseases. The difference was significant ($\chi^2 = 10.54$ $p < 0.01$)

No significant difference between boys and girls was noted in the frequency of functional symptoms. Table 22.

AGE

12.0 per cent of the present series of children were less than 1 month old, 21.6 per cent 1—11 months, 42.3 per cent pre-school age (1—6 years) and 23.7 per cent school age (7—15 years)

For the statistical test the children were divided into two groups those up to

TABLE 21

INDICATIONS FOR HOSPITAL ADMISSION OF THE CHILD

	Mental disorders	Functional symptoms	Other diseases	Total
Purely medical	182 (2.5 %)	507 (7.1 %)	6457 (90.4 %)	7146 (100 %)
Partly or decisively social	43 (7.7 %)	31 (5.6 %)	483 (86.7%)	557 (100 %)
Partly or decisively due to psychological factors in the family	40 (21.7 %)	50 (27.2 %)	94 (51.1 %)	184 (100 %)
Total	265 (3.4 %)	588 (7.4 %)	7034 (89.2 %)	7887 (100 %)

Not reported	67
	7954
Non-response rate	0.3 %

TABLE 22

SEX DISTRIBUTION

	Mental disorders	Functional symptoms	Other diseases	Total series
Girls	88 (2.6 %)	265 (7.7 %)	3080 (89.7 %)	3433 (100.0 %)
Boys	175 (3.9 %)	321 (7.2 %)	3980 (88.9 %)	4476 (100.0 %)
Total	263 (3.3 %)	586 (7.4 %)	7060 (89.3 %)	7909 (100.0 %)

Not reported	45
	7954
Non-response rate	0.6 %

TABLE 23

AGE OF THE CHILD

	Mental disorders		Functional symptoms		Other diseases	Total series
Under 1 month	2	(0.2 %)	57	(6.1 %)	882 (93.7 %)	941 (100.0)
1—11 months	5	(0.3 %)	77	(4.6 %)	1606 (95.1 %)	1688 (100.0 %)
1—6 yrs	118	(3.5 %)	230	(6.9 %)	2987 (89.6 %)	3335 (100.0 %)
7—15 yrs	139	(7.5 %)	214	(11.6 %)	1497 (80.9 %)	1850 (100.0 %)
Total	264	(3.4 %)	578	(7.4 %)	6972 (89.2 %)	7814 (100.0 %)

Not reported	140
	7954
Non-response rate	1.8 %

11 months, and those of one or more than one year

Psychic diseases were the main diagnosis for fewer infants (1—11 months) than for children of 1—15 years. The difference was highly significant ($\chi^2 = 116.13$, $p < 0.001$) The percentage of school age children (7—15 years) was highest, 7.5 per cent

Admissions for functional symptoms of children aged more than 1 year were more frequent than those of infants. The difference was highly significant ($\chi^2 = 30.09$, $p < 0.001$) In the admissions for functional symptoms also, the largest individual age group was that of 7—15 years (11.6 per cent) even though these diagnoses occurred among infants under 1 month (6.1 per cent) whereas psychic diseases were very infrequent (0.2 per cent) in this age group.

There were more mental disorders in the age group of 7—15 years than under 7 years old. The difference was highly significant ($\chi^2 = 139.6$, $p < 0.001$) In the functional symptoms group there were also more children between 7 and 15 years than under 7 years. The difference was highly significant ($\chi^2 = 72.8$, $p < 0.001$) Table 23

LEGITIMACY OF THE CHILD

4.3 per cent of the children of the present series were born out of wedlock while 95.7 per cent had parents who were married.

A comparison of the percentages of illegitimate and legitimate children in the admissions for psychic diseases and those for functional symptoms revealed no significant differences. In other words, admissions of illegitimate children for psychic diseases or functional symptoms were no more frequent or infrequent than those of legitimate children.

SENIORITY AMONG SIBLINGS

25.9 per cent of the present series of children were only children of their families, 14.1 per cent were eldest children, while 60 per cent were second, third etc. eldest.

Admissions for psychic diseases less frequently concerned the only child than one of several siblings. The difference was highly significant ($\chi^2 = 56.92$, $p < 0.001$) The same was true of admissions for functional symptoms. The difference was highly significant ($\chi^2 = 48.93$, $p < 0.001$)

From testing the eldest child against the others (second etc. eldest and the only child) it was found that eldest children were admitted for psychic symptoms more often than other children. The difference was almost significant ($\chi^2 = 5.37$, $p < 0.001$) In the functional symptoms

TABLE 24

SENIORITY OF THE CHILD AMONG SIBLINGS

	Mental disorders		Functional symptoms		Other diseases		Total series
Only child	43	(2.1)	147	(7.2)	1861	(90.7)	2051 (100.0)
Eldest	56 }*	(5.0)	92 }	(8.3)	965	(86.7)	1113 (100.0)*
Second eldest etc.	166 }	(3.5)	249 }	(7.4)	4226	(89.1)	4741 (100.0)
Total	265	(3.4)	388	(7.4)	7052	(89.2)	7903 (100.0)
					Not reported		49
							7954
					Non-response rate		0.6 %

TABLE 21

INDICATIONS FOR HOSPITAL ADMISSION OF THE CHILD

	Mental disorders	Functional symptoms	Other diseases	Total
Purely medical	182 (2.5 %)*	507 (7.1 %)	6457 (90.4 %)	7146 (100 %)
Partly or decisively social	43 (7.7 %)	31 (5.6 %)	483 (86.7 %)	557 (100 %)
Partly or decisively due to psychological factors in the family	40 (21.7 %)	50 (27.2 %)	94 (51.1 %)	184 (100 %)
Total	265 (3.4 %)	588 (7.4 %)	7034 (89.2 %)	7887 (100 %)
			Not reported	67
				7954
			Non response rate	0.3 %

TABLE 22

SEX DISTRIBUTION

	Mental disorders	Functional symptoms	Other diseases	Total series
Girls	88 (2.6 %)	265 (7.7 %)	3080 (89.7 %)	3433 (100.0 %)
Boys	175 (3.9 %)	321 (7.2 %)	3980 (88.9 %)	4476 (100.0 %)
Total	263 (3.3 %)	586 (7.4 %)	7060 (89.3 %)	7909 (100.0 %)
			Not reported	45
				7954
			Non-response rate	0.6 %

TABLE 23

AGE OF THE CHILD

	Mental disorders		Functional symptoms		Other diseases	Total series
Under 1 month	2	(0.2 %)	57	(6.1 %)	882 (93.7 %)	911 (100.0 %)
1—11 months	5	(0.3 %)	77	(4.6 %)	1606 (95.1 %)	1688 (100.0 %)
1—6 yrs	118	(3.5 %)	230	(6.9 %)	2987 (89.6 %)	3335 (100.0 %)
7—15 yrs	139	(7.5 %)	214	(11.6 %)	1497 (80.9 %)	1850 (100.0 %)
Total	264	(3.4 %)	578	(7.4 %)	6972 (89.2 %)	7814 (100.0 %)
					Not reported	140
						7954
					Non-response rate	1.8 %

11 months, and those of one or more than one year

Psychic diseases were the main diagnosis for fewer infants (1—11 months) than for children of 1—15 years. The difference was highly significant ($\chi^2 = 116.13$ $p < 0.001$) The percentage of school age children (7—15 years) was highest, 7.5 per cent.

Admissions for functional symptoms of children aged more than 1 year were more frequent than those of infants. The difference was highly significant ($\chi^2 = 30.09$ $p < 0.001$) In the admissions for functional symptoms also the largest individual age group was that of 7—15 years (11.6 per cent) even though these diagnoses occurred among infants under 1 month (6.1 per cent) whereas psychic diseases were very infrequent (0.2 per cent) in this age group

There were more mental disorders in the age group of 7—15 years than under 7 years old. The difference was highly significant ($\chi^2 = 139.6$, $p < 0.001$) In the functional symptoms group there were also more children between 7 and 15 years than under 7 years. The difference was highly significant ($\chi^2 = 72.8$, $p < 0.001$) Table 23

LEGITIMACY OF THE CHILD

4.3 per cent of the children of the present series were born out of wedlock while 95.7 per cent had parents who were married.

A comparison of the percentages of illegitimate and legitimate children in the admissions for psychic diseases and those for functional symptoms revealed no significant differences. In other words, admissions of illegitimate children for psychic diseases or functional symptoms were no more frequent or infrequent than those of legitimate children.

SENIORITY AMONG SIBLINGS

25.9 per cent of the present series of children were only children of their families, 14.1 per cent were eldest children, while 60 per cent were second, third etc. eldest.

Admissions for psychic diseases less frequently concerned the only child than one of several siblings. The difference was highly significant ($\chi^2 = 56.92$, $p < 0.001$) The same was true of admissions for functional symptoms. The difference was highly significant ($\chi^2 = 48.93$ $p < 0.001$)

From testing the eldest child against the others (second etc. eldest and the only child) it was found that eldest children were admitted for psychic symptoms more often than other children. The difference was almost significant ($\chi^2 = 5.37$ $p < 0.001$) In the functional symptoms

TABLE 24

SENIORITY OF THE CHILD AMONG SIBLINGS

	Mental disorders		Functional symptoms		Other diseases		Total series
Only child	45	(2.1)	147	(7.2)	1861	(90.7)	2051 (100.0)
Eldest	56	(5.0)	92	(8.3)	963	(86.7)	1113 (100.0)***
Second eldest etc.	166	(3.5)	249	(7.4)	4226	(89.1)	4741 (100.0)
Total	263	(3.4)	583	(7.4)	7052	(90.2)	7805 (100.0)
					Not reported		49
							7854
					Non-response rate		0.6 %

group the difference between the eldest and the other children was not significant Table 24

Factors connected with the family and home

FATHER'S OCCUPATIONAL STATUS

49 4 per cent of the fathers of the present series of children were workers while the remainder belonged to groups shown in Table 25

Frequencies of psychic diseases and functional symptoms did not differ between the workers and the others

EDUCATIONAL LEVEL OF FATHER

80 0 per cent of the fathers of the present series of children had only passed through the primary school 14 2 per cent had matriculated 5 8 per cent had an academic degree.

For the statistical test the fathers were divided into those with primary school education and others

Admissions for psychic diseases or functional symptoms were not fewer or more numerous among children of fathers with primary school than among those with more educated fathers

When fathers with an academic degree were tested against others there were more mental disorders in children of academic fathers than in children of other fathers The difference was almost significant ($\chi^2 = 5.6$ $p < 0.05$) Table 26

FATHER'S MARITAL STATUS

90 2 per cent of the fathers of the present series of children were married 4 1 per cent were unmarried widowed or divorced and 5 7 per cent dead or not known

For the statistical test the children of unmarried widowed or divorced fathers and the children whose father was dead or whose father's marital status was unknown were added together This group was tested against the children of married fathers

Admissions for psychic diseases of the children of single fathers were more frequent than of married fathers. The difference was highly significant ($\chi^2 = 16.73$ $p < 0.001$) Since the percentages for married fathers (3 0 per cent) and dead or unknown fathers (2 9 per cent) were of the same magnitude the difference is mainly derived from the share of the solitary (unmarried widowed or divorced) fathers (10 2 per cent)

Admissions for functional symptoms revealed no significant difference between these two groups of fathers Table 27

TABLE 2[illegible]

FATHER'S OCCUPATIONAL STATUS

	Mental disorders	Functional symptoms	Other diseases	Total
Worker	137 (3 5 %)	202 (7 2)	3511 (89 3)	3930 (100)
Self-employed	53 (3.0 %)	120 (7 8 %)	1561 (88.7)	1 31 (100)
Manager executive	52 (2 9 %)	127 (7 2 %)	1588 (89 9)	1767 (100)
Assisting family member	0	1 (14 3 %)	6 (8 7)	7 (100)
Independent without occupation student inmate of an institution, dead or not known	3 (3.2 %)	58 (8.1)	635 (88.7)	716 (100 %)
Total	265 (3 3 %)	588 (7 4 %)	7101 (89 3)	7954 (100 %)

TABLE 26

ATERNAL EDUCATIONAL LEVEL

	Mental disorders	Functional symptoms	Other diseases	Total series
1—3	191 (3.4 %)	423 (7.4 %)	5084 (89.2 %)	5698 (100 %)
4—7	19 (1.9 %)	79 (7.8 %)	919 (90.3 %)	1017 (100 %)
8	22 (5.4 %)	34 (8.3 %)	355 (86.3 %)	411 (100 %)
Total	232 (3.3 %)	536 (7.5 %)	6358 (89.2 %)	7126 (100 %)
			Not reported	828
				7954
			Non-response rate	10.4

1—3 = primary school
4 = secondary school, lower forms
5 = secondary school, five forms (middle school)
6 = secondary school, more than five forms but no matriculation
7 = matriculation but no university or other degree
8 = university or other degree

TABLE 27

THEIR MARITAL STATUS

	Mental disorders	Functional symptoms	Other diseases	Total series
Married	219 (3.0 %)	536 (7.5 %)	6418 (89.5 %)	7173 (100 %)
Solitary	33 (10.2 %)	25 (7.7 %)	267 (82.1 %)	325 (100 %)
Dead or not know	13 (2.9 %)	27 (5.9 %)	416 (91.2 %)	456 (100 %)
Total	265 (3.3 %)	588 (7.4 %)	7101 (89.3 %)	7954 (100 %)

TABLE 28

THE AGGREGATE MONTHLY EARNINGS OF THE ...

	Mental disorders	Functional symptoms	Other diseases	Total series
≤ 1000 mk	154 (3.0 %)	382 (7.4 %)	4631 (89.6 %)	5167 (100.0 %)
1000 mk	47 (4.2 %)	96 (8.6 %)	977 (87.2 %)	1120 (100.0 %)
Farmer family	39 (3.9 %)	68 (6.7 %)	902 (89.4 %)	1009 (100.0 %)
Total	240 (3.3 %)	546 (7.5 %)	6510 (89.2 %)	7296 (100.0 %)
			Not reported	658
				7954
			Non-response rate	8.3

3

group the difference between the eldest and the other children was not significant. Table 24

Factors connected with the family and home

FATHER'S OCCUPATIONAL STATUS

49 4 per cent of the fathers of the present series of children were workers, while the remainder belonged to groups shown in Table 25

Frequencies of psychic diseases and functional symptoms did not differ between the workers and the others

EDUCATIONAL LEVEL OF FATHER

80 0 per cent of the fathers of the present series of children had only passed through the primary school 14 2 per cent had matriculated 5 8 per cent had an academic degree

For the statistical test the fathers were divided into those with primary school education and others.

Admissions for psychic diseases or functional symptoms were not fewer or more numerous among children of fathers with primary school than among those with more educated fathers

When fathers with an academic degree were tested against others there were more mental disorders in children of academic fathers than in children of other fathers. The difference was almost significant ($\chi^2 = 5\ 6$ $p < 0\ 05$) Table 26

FATHER'S MARITAL STATUS

90 2 per cent of the fathers of the present series of children were married, 4 1 per cent were unmarried widowed or divorced and 5 7 per cent dead or not known

For the statistical test the children of unmarried widowed or divorced fathers and the children whose father was dead or whose father's marital status was unknown were added together This group was tested against the children of married fathers.

Admissions for psychic diseases of the children of single fathers were more frequent than of married fathers. The difference was highly significant ($\chi^2 = 16.73$ $p < 0\ 001$) Since the percentages for married fathers (3 0 per cent) and dead or unknown fathers (2 9 per cent) were of the same magnitude the difference is mainly derived from the share of the solitary (unmarried widowed or divorced) fathers (10 2 per cent)

Admissions for functional symptoms revealed no significant difference between these two groups of fathers Table 27

TABLE 25

FATHER'S OCCUPATIONAL STATUS

	Mental disorders	Functional symptoms	Other diseases	Total
Worker	137 (3 5 %)	282 (7 2)	3511 (89 3)	3930 (100)
Self-employed	53 (3.5 %)	120 (7.8)	1361 (88.7)	1534 (100)
Manager executive	52 (2 9 %)	127 (7 2)	1588 (89.9)	1767 (100)
Assisting family member	0	1 (14 3)	6 (85.7)	7 (100)
Independent without occupation, student, inmat of an institution, dead or not known	23 (3.2 %)	58 (8.1)	635 (88.7)	716 (100)
Total	265 (3.3 %)	588 (7 4 %)	7101 (89 3)	7954 (100)

TABLE 26

TERMAL EDUCATIONAL LEVEL

	Mental disorders		Functional symptoms		Other diseases		Total series	
1—5	191	(3.4 %)	423	(7.4 %)	5084	(89.2 %)	5698	(100)
4—7	19	(1.9)	79	(7.8 %)	919	(90.3 %)	1017	(100 %)
8	22	(5.4 %)	34	(8.3 %)	355	(86.3 %)	411	(100 %)
Total	232	(3.3 %)	536	(7.5)	6358	(89.2 %)	7126	(100 %)
					Not reported		828	
							7954	
					Non-response rate		10.4	

1—3 = primary school
4 = secondary school, lower forms
5 = secondary school, five forms (middle school)
6 = secondary school, more than five forms but no matriculation
7 = matriculation but no university or other degree
8 = university or other degree

TABLE 27

THEIR MARITAL STATUS

	Mental disorders		Functional symptoms		Other diseases		Total series	
Married	219	(3.0)	536	(7.5)	6418	(89.5)	7173	(100 %)
Solitary	33	(10.2 %)	25	(7.7)	267	(82.1 %)	325	(100 %)
Dead or not know	13	(2.9 %)	27	(5.9 %)	416	(91.2 %)	456	(100 %)
Total	265	(3.3)	588	(7.4)	7101	(89.3)	7954	(100 %)

TABLE 28

THE AGGREGATE MONTHL EARNINGS THE PARENTS

	Mental disorders		Functional symptoms		Other diseases		Total series	
≤ 1000 mk	154	(3.0 %)	382	(7.4 %)	4631	(89.6 %)	5167	(100.0 %)
1000 mk	47	(4.2 %)	96	(8.6)	977	(87.2 %)	1120	(100.0 %)
Farmer family	39	(3.9 %)	68	(6.7 %)	902	(89.4 %)	1009	(100.0 %)
Total	240	(3.3 %)	546	(7.5 %)	6510	(89.2)	7296	(100.0 %)
					Not reported		658	
							7954	
					Non-response rate		8.3	

7[illegible] per cent of the parents of the present series of *children had monthly* income of maximum 1000 mk. 15.[illegible] per cent over 1000 mk. and [illegible] per cent were farmers.

The testing was carried out in two stages. In the first, frequency of mental disorders in children from farming families was compared with that in children from non-farming families. The difference was not significant nor was it for functional symptoms.

In the second test children from farming families were excluded and the frequencies of mental disorders and functional symptoms were compared in the two income classes. Mental disorders [illegible] primary diagnoses were more prevalent in children from upper [illegible] per cent than lower [illegible]0 per cent [illegible]. The difference was almost [illegible] = 4.01 p < 0.05 Table [illegible].

NUMBER OF INHABITANTS PER [illegible] THE FAMILY

40.1 per cent of the [illegible] present series of children [illegible] person per room. [illegible]2.1 per cent [illegible] families with a living density [illegible] persons per room. and 7.3 per cent [illegible] families with a living density [illegible] persons per room. 0.[illegible] per cent [illegible] inhabitant per room.

The group with one [illegible] room was compared in the [illegible] with the families with a [illegible] of more than one per room.

In the psychic diseases group [illegible] between these two living [illegible]

[illegible]

[illegible]	[illegible]					[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
[illegible]				[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]		[illegible]			[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

[illegible]

[illegible]

[illegible]	[illegible]				[illegible]	[illegible]	[illegible]
[illegible]	[illegible]				[illegible]	[illegible]	[illegible]
[illegible]	[illegible]				[illegible]	[illegible]	[illegible]

[illegible]

[illegible]

groups were not significant. The functional symptoms group contained more children of families with one inhabitant per room than of families with more than one inhabitant per room. The difference was almost significant ($\chi^2 = 4.99$ $p < 0.05$) Table 29

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents of the present series of children owned a private car while 68.4 per cent did not.

A comparison between car owners and non-owners revealed no significant differences in admissions for psychic diseases or in admissions for functional symptoms.

TELEVISION SET AT HOME

42.2 per cent of the homes of the present series of children had TV

Admissions for psychic diseases of children from *families with* TV were more frequent than those of children from families without TV The difference was *almost* significant ($\chi^2 = 5.52$, $p < 0.05$)

In the functional symptoms group a similar difference was noted children with TV at home were admitted more frequently than those who had no TV at home The difference was almost significant ($\chi^2 = 5.78$, $p < 0.05$) Table 30

OWNERSHIP OF A SUMMER COTTAGE

9.8 per cent of the parents of the present series of children had a summer cottage

Children of families with a summer cottage were admitted more frequently *for psychic diseases* than those of families without summer cottage The difference was almost significant ($\chi^2 = 5.39$ $p < 0.05$)

The functional symptoms group revealed a similar difference children of families with summer cottage were admitted more frequently than those of families without summer cottage. The difference was highly significant ($\chi^2 = 10.97$ $p < 0.001$) Table 31

DISTANCE BETWEEN CHILD'S *HOME AND* PHYSICIAN'S OFFICE

46.5 per cent of the present series of children lived at a maximum distance of 1 km from the physician's office 16.2 per cent *at* 2—3 km, 17.7 *per cent at* 4—10 km and 19.6 per cent at more than 10 km distance.

Testing was carried out in two stages 1 less than 1 km vs. more than 1 km 2 less than 10 km vs. more than 10 km

No significant differences were found between these groups in either psychic diseases or functional symptoms.

DISTANCE BETWEEN HOME AND HOSPITAL

46.2 per cent of the present series of children lived at a maximum distance of 10 km from the hospital, 38.3 *per cent* at 11—100 km, and 15.5 per cent over 100 km

The *testing was* carried out in two stages 1 maximum 10 km vs. more than

TABLE 31

OWNERSHIP SUMMER COTTAGE

	Mental disorders		Functional symptoms		Other diseases		Total series	
Summer cottage	33	4.9	76	10.6	608	84.5	719	(100.0)
Summer cottage	209	3.2	469	(7.1)	5943	(89.7)	6621	(100.0)
Total	244	3.3	[illegible]	(7.4)	6551	(89.3)	7340	(100.0)
					Not reported		614	
							7954	
					Nonresponse rate		7.7	

AGGREGATE INCOME

70 8 per cent of the parents of the present series of children had monthly incomes of maximum 1000 mk, 15 4 per cent over 1000 mk, and 13 8 per cent were farmers.

The testing was carried out in two stages In the first, frequency of mental disorders in children from farming families was compared with that in children from non farming families The difference was not significant nor was it for functional symptoms.

In the second test children from farming families were excluded and the frequencies of mental disorders (and functional symptoms) were compared in the two income classes Mental disorders (as primary diagnoses) were more prevalent in children from upper (4 2 per cent) than lower (3 0 per cent) income families. The difference was almost significant ($\chi^2 = 4\,01$ $p < 0\,05$) Table 28

NUMBER OF INHABITANTS PER ROOM IN THE FAMILY

40 1 per cent of the homes of the present series of children housed one person per room 52 1 per cent were families with a living density of 2—3 persons per room and 7 3 per cent were families with a living density of 4—6 persons per room 0 5 per cent had over 6 inhabitants per room

The group with one inhabitant per room was compared in the statistical test with the families with a living density of more than one per room

In the psychic diseases group the differences between these two living density

TABLE 29

NUMBER OF INHABITANTS PER ROOM IN THE FAMILY

	Mental disorders		Functional symptoms		Other diseases		Total series	
1 person	99	(3 4)	24	(8.3 *)	2596	(88.3 *)	2940	(100)
2 3 persons	127	(3.3)	254	(6 7)	3434	(90.0)	3815	(100)
4 6 persons	13	(2 4)	44	(8.2)	482	(89 4)	539	(100)
Over 6 persons	2	(9)	5	(14 7)	27	(79 4)	34	(100)
Total	241	(3 3)	548	(7 5)	6539	(89 2)	7328	(100
					Not reported		626	
							7954	
					Non-response		7 9	

TABLE 30

TELEVISION T A OM

	Mental disorders		Functional symptoms		Other disease		Total series	
Television	124	(4 0)	262	(8 3)	755	(87 7)	3141	(100.0
Television —	126	(2 9 *)	294	(6.8)	3884	(90.3)	4304	(100 0)
Total	250	(3 3)	556	(7 5)	6639	(89 2)	7445	(100.0)
					Not reported		509	
							7954	
					Non-response		6 4	

groups were not significant. The functional symptoms group contained more children of families with one inhabitant per room than of families with more than one inhabitant per room. The difference was almost significant ($\chi^2 = 4.99$, $p < 0.05$) Table 29

OWNERSHIP OF A PRIVATE CAR

31.6 per cent of the parents of the present series of children owned a private car while 68.4 per cent did not.

A comparison between car owners and non-owners revealed no significant differences in admissions for psychic diseases or in admissions for functional symptoms.

TELEVISION SET AT HOME

42.2 per cent of the homes of the present series of children had TV.

Admissions for psychic diseases of children from families with TV were more frequent than those of children from families without TV. The difference was almost significant ($\chi^2 = 5.52$, $p < 0.05$)

In the functional symptoms group a similar difference was noted: children with TV at home were admitted more frequently than those who had no TV at home. The difference was almost significant ($\chi^2 = 5.78$, $p < 0.05$) Table 30

OWNERSHIP OF A SUMMER COTTAGE

9.8 per cent of the parents of the present series of children had a summer cottage.

Children of families with a summer cottage were admitted more frequently for psychic diseases than those of families without summer cottage. The difference was almost significant ($\chi^2 = 5.39$, $p < 0.05$)

The functional symptoms group revealed a similar difference: children of families with summer cottage were admitted more frequently than those of families without summer cottage. The difference was highly significant ($\chi^2 = 10.97$, $p < 0.001$) Table 31

DISTANCE BETWEEN CHILD'S HOME AND PHYSICIAN'S OFFICE

46.5 per cent of the present series of children lived at a maximum distance of 1 km from the physician's office, 16.2 per cent at 2—3 km, 17.7 per cent at 4—10 km, and 19.6 per cent at more than 10 km distance.

Testing was carried out in two stages: 1. less than 1 km vs. more than 1 km, 2. less than 10 km vs. more than 10 km.

No significant differences were found between these groups in either psychic diseases or functional symptoms.

DISTANCE BETWEEN HOME AND HOSPITAL

46.2 per cent of the present series of children lived at a maximum distance of 10 km from the hospital, 38.3 per cent at 11—100 km, and 15.5 per cent over 100 km.

The testing was carried out in two stages: 1. maximum 10 km vs. more than

TABLE 31

OWNERSHIP OF SUMMER COTTAGE

	Mental disorders		Functional symptoms		Other diseases		Total series	
Summer cottage	35	(4.9)	76	(10.6)***	608	(84.5)	719	(100.0)
No summer cottage	209	(3.2)	469	(7.1)**	5943	(89.7)	6621	(100.0)
Total	244	(3.3)	545	(7.4)	6551	(89.3)	7340	(100.0)
					Not reported		614	
							7954	
					Non-response rate		7.7	

TABLE 3

DISTANCE OF CHILD'S HOME FROM HOSPITAL

	Mental disorders		Functional symptoms		Other diseases		Total series	
≦ 10 km	72	(2.1)	253	(7 2)	3161	(90.7 %)	3486	(100.0 %)
11—100 km	114	(3 9)	186	(6.4 %)	2596	(89 7)	2896	(100.0)
> 100 km	71	(6.0)	121	(10.3)	982	(83.7 %)	1174	(100.0)
Total	257	(3.4)	560	(7 4)	6739	(89.2 %)	7556	(100.0)
					Not reported		398	
							7954	
					Non response rate		5.0	

10 km 2 maximum 100 km vs. more than 100 km

Admissions for psychic diseases of children living at a maximum 10 km distance from the hospital were fewer than those of children more than 10 km distant from hospital The difference was highly significant ($\chi^2 = 34\ 40$ $p < 0\ 001$) In admissions for functional symptoms the differences were not significant between those living at maximum 10 km and those living more than 10 km distant from hospital

The psychic diseases group contained a larger number of children living more than 100 km distant from hospital than those living at a maximum 100 km distance The difference was highly significant ($\chi^2 = 28\ 68$ $p < 0\ 001$) The functional symptoms group also contained a larger number of children living at a distance of more than 100 km from hospital. The difference was highly significant ($\chi^2 = 16\ 48$ $p < 0\ 001$) Table 32

TYPE OF RESIDENTIAL COMMUNE

21 7 per cent of the present series of children came from Helsinki, 29 4 per cent from the other towns 6 5 per cent from market boroughs and 12 4 per cent from rural districts

For statistical testing the children from Helsinki and other towns were combined (= urban 51 1 per cent) and those from market boroughs and rural districts were also combined (= rural 48.9 per cent)

No significant differences were noted in the frequency of admissions for psychic diseases or functional symptoms between urban and rural children

When the Helsinki children were tested vs all others, there was no significant difference between these groups in the frequency of admissions for psychic diseases. In admissions for functional symptoms, more children from Helsinki than from other localities were among the admitted The difference was almost significant ($\chi^2 = 4\ 78$ $p < 0\ 051$) Table 33

Factors connected with the hospital

SOUTH OR NORTH FINLAND

18 2 per cent of the present series of children came from North Finland (for definition see p 19 above) and 81 8 per cent from South Finland

The numbers of children coming from North and South Finland revealed no significant differences in admissions for psychic diseases. In other words, the number of children admitted for psychic diseases from North Finland was significantly neither higher nor lower than that admitted from South Finland

Admissions for functional symptoms of children from North Finland were more numerous than from South Finland The difference was highly significant ($\chi^2 = 53\ 98$ $p < 0\ 001$) Table 34

TABLE 33

TYPE OF CHILD DOMICILE

	Mental disorders		Functional symptoms		Other diseases		Total series	
Helsinki	49	(2.9 %)	149	(8.6 %)	1525	(88.5 %)	1723	(100.0)
Other city	73	(3.1 %)	168	(7.2 %)	2094	(89.7 %)	2335	(100.0 %)
Other urban district	18	(3.5 %)	32	(6.2 %)	466	(90.3 %)	516	(100.0)
Rural district	125	(3.7 %)	239	(7.1 %)	3010	(89.2 %)	3374	(100.0)
Total	263	(3.3 %)	588	(7.4 %)	7095	(89.3 %)	7948	(100.0)

TABLE 34

SOUTH FINLAN AND NORTH FINLAND

	Mental disorders		Functional symptoms		Other diseases		Total series	
South Finland	214	(3.4 %)	404	(6.3 %)**	5759	(90.3 %)	6377	(100.0 %)
North Finland	46	(3.2 %)	170	(12.0)	1204	(84.8 %)	1420	(100.0)
Total	260	(3.3 %)	574	(7.4)	6963	(89.3 %)	7797	(100.0)
					Not reported		157	
							7954	
					Non-response rate		2.0 %	

TABLE 35

DISTRIBUTION TIENTS ACCORDING TO TYPE HOSPITAL

	Mental disorders		Functional symptoms		Other diseases		Total series	
University teaching hospitals and Children Castle Helsinki	154	(6.9)	187	(8.3 %)	1899	(84.8 %)	2240	(100.0
City Hospital of Helsinki (Aurora	15	(1.2 %)*	103	(8.4)	1110	(90.4)	1228	(100.0
Hospitals with several pediatricians	67	(2.5	209	(7.7)	2443	(89.8 %)	2719	(100.0)
Hospitals with one pediatrician	29	(1.7) **	88	(5.2 %)	1574	(93.1)	1691	(100.0)
Total	263	(3.4)	587	(7.4 %	7026	(89.2 %)	7878	(100.0)
					Not reported		76	
							7954	
					Non-response rate		1.0 %	

HOSPITAL TYPE

28.4 per cent of the present series of children had been treated at university central hospitals and the Children's Castle of Helsinki (= Type 1), 15.6 per cent in City Hospital of Helsinki, 34.5 per cent in hospitals with two or more pediatricians and 21.5 per cent in units with one pediatrician.

Each hospital type was tested against the others.

Admissions for psychic diseases to hospitals of Type 1 were more frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 117.20$, $p < 0.001$).

Admissions for psychic diseases to City Hospital of Helsinki (= Type 2) were less frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 19.77$, $p < 0.001$).

Admissions for psychic diseases to hospitals with two or more pediatricians were less frequent than to the other hospitals. The difference was significant ($\chi^2 = 9.92$, $p < 0.01$).

Admissions for psychic diseases to hospitals with one pediatrician were also less frequent than admissions to the other hospitals. The difference was highly significant ($\chi^2 = 17.37$, $p < 0.001$).

Only one type of hospital was significantly different from the others in the frequency of admissions for functional symptoms: units with one pediatrician had a lower frequency than the other hospitals. The difference was highly significant ($\chi^2 = 15.35$, $p < 0.001$) (Table 35).

ADMISSION DELAY

87.2 per cent of the present series of children did not have to wait at all for admission, 4.3 per cent waited for a maximum of one week, 3.4 per cent for 8—30 days, and 5.1 per cent for more than a month.

Table 37 gives the percentages of admission delays by diagnostic groups. While only 5.1 per cent of the total series had to wait for admission for more than a month, the corresponding figure among admissions for psychic diseases was 31.3 per cent. While 3.4 per cent of the total series waited for 8—30 days, the figure among admissions for psychic diseases was 15.1 per cent.

When those with no delay in admission were tested against all others it was found that there were fewer undelayed admissions in the psychic diseases group. The difference was highly significant ($\chi^2 = 382.57$, $p < 0.001$).

A similar difference was seen in admissions for functional diseases: children were admitted less frequently without delay than after a period of queuing up. The difference was highly significant ($\chi^2 = 17.11$, $p < 0.001$).

When the group of children who had had to wait for a maximum of one month was tested against that with a waiting period exceeding one month, it was found that children had had to wait for admission for psychic diseases more frequently for more than a month than for a month. The difference was highly significant ($\chi^2 = 385.94$, $p < 0.001$).

Children with functional symptoms had had to wait for more than a month less frequently than for a maximum of a month. The difference was highly significant ($\chi^2 = 275.39$, $p < 0.001$) (Table 36).

POSSIBILITIES OF AN EARLIER DISCHARGE

For purely medical, therapeutic reasons, 90.1 per cent of the present series of children could not have been discharged earlier, while 9.9 per cent had some factors prolonging their stay in hospital. The biggest group among these factors was difficult home conditions (4.5 per cent of the total series).

A larger proportion of the children kept in hospital for not purely medical therapy had been admitted for psychic diseases than of the children with no additional indications. The difference was highly significant ($\chi^2 = 13.58$, $p < 0.001$).

The percentages of admissions for functional symptoms did not differ significantly between these two groups. But in the group of children who had to wait for examination the percentage of functional symptoms (28.2 per cent) was relatively high (Table 38).

TABLE 36

HOW LONG DI THE CHILD HAVE TO WAIT FOR DMISSIO ?

	Mental disorders		Functional symptoms		Other diseases		Total series	
Not at all	196	(1.8 %)	480	(6.9 %) **	6350	(91.3 „)	6936	(100.0)
≤ 7 day	16	(4.7 „)	45	(13.1 „)	282	(82.2 „)	343	(100.0)
8–30 day	40	(14.8 %)	29	(10.7)	202	(74.5)	271	(100.0)
1 month	83	(20.5 „)	34	(8.4 %)	287	(71.1 %)	404	(100.0)
Total	265	(3.3 „)	588	(7.4 %)	7101	(89.3 %)	7954	(100.0)

TABLE 37

THE CHILD WAITING TIME (= ADMISSIO DELA) IN IFFERENT DIAGNOSTIC GROUPS

	Mental disorders	Functional symptoms %	Other diseases „	Total series %
Not at all	47.6	81.6	89.2	87.2
≤ 7 days	6.0	7.7	4.0	4.3
8–30 day	15.1	4.9	2.8	3.4
1 month	31.3	5.8	4.0	5.1
Total	100.0	100.0	100.0	100.0

TABLE 38

CO THE CHIL HA BEEN DISCHARGE EARLIER

	Mental disorders		Functional symptoms		Other diseases		Total series	
N	148	2.3	472	(7.4)	5743	(90.3)	6363	(100.0
Yes, if the child's home had been better	13	(4.1	6	(1.9)	299	(94.0	318	(100.0
Yes, if the child's home had been nearer located	3	4.0	3	4.0)	68	(92.0)	74	(100.0)
Yes, if the child had not acquired an infection in the hospital	3	(4.2)	2	(2.8 „)	67	(93.0)	72	(100.0)
Yes, if there had been an ation period before examinations	7	6.8)	29	(28.2)	67	(65.0)	103	(100.0)
Yes, if certain other conditions had been met	7	(5.3	14	10.7)	110	(84.0 „)	131	(100.0 %)
Total	181	(2.6	526	(7.4)	6354	(90.0)	7061	(100.0 %)
					Not reported		893	
							7954	
					Non-response rate		11.2	

HOSPITAL TYPE

28.4 per cent of the present series of children had been treated at university central hospitals and the Children's Castle of Helsinki (= Type 1), 15.6 per cent in City Hospital of Helsinki, 34.5 per cent in hospitals with two or more pediatricians and 21.5 per cent in units with one pediatrician.

Each hospital type was tested against the others.

Admissions for psychic diseases to hospitals of Type 1 were more frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 117.20$, $p < 0.001$).

Admissions for psychic diseases to City Hospital of Helsinki (= Type 2) were less frequent than to the other hospitals. The difference was highly significant ($\chi^2 = 19.77$, $p < 0.001$).

Admissions for psychic diseases to hospitals with two or more pediatricians were less frequent than to the other hospitals. The difference was significant ($\chi^2 = 9.92$, $p < 0.01$).

Admissions for psychic diseases to hospitals with one pediatrician were also less frequent than admissions to the other hospitals. The difference was highly significant ($\chi^2 = 17.37$, $p < 0.001$).

Only one type of hospital was significantly different from the others in the frequency of admissions for functional symptoms: units with one pediatrician had a lower frequency than the other hospitals. The difference was highly significant ($\chi^2 = 15.35$, $p < 0.001$). Table 35.

ADMISSION DELAY

87.2 per cent of the present series of children did not have to wait at all for admission, 4.3 per cent waited for a maximum of one week, 3.4 per cent for 8—30 days, and 5.1 per cent for more than a month.

Table 37 gives the percentages of admission delays by diagnostic groups. While only 5.1 per cent of the total series had to wait for admission for more than a month, the corresponding figure among admissions for psychic diseases was 31.3 per cent. While 3.4 per cent of the total series waited for 8—30 days the figure among admissions for psychic diseases was 15.1 per cent.

When those with no delay in admission were tested against all others it was found that there were fewer undelayed admissions in the psychic diseases group. The difference was highly significant ($\chi^2 = 382.57$, $p < 0.001$).

A similar difference was seen in admissions for functional diseases: children were admitted less frequently without delay than after a period of queuing up. The difference was highly significant ($\chi^2 = 17.11$, $p < 0.001$).

When the group of children who had had to wait for a maximum of one month was tested against that with a waiting period exceeding one month, it was found that children had had to wait for admission for psychic diseases more frequently for more than a month than for a month. The difference was highly significant ($\chi^2 = 385.94$, $p < 0.001$).

Children with functional symptoms had had to wait for more than a month less frequently than for a maximum of a month. The difference was highly significant ($\chi^2 = 275.39$, $p < 0.001$). Table 36.

POSSIBILITIES OF AN EARLIER DISCHARGE

For purely medical, therapeutic reasons 90.1 per cent of the present series of children could not have been discharged earlier, while 9.9 per cent had some factors prolonging their stay in hospital. The biggest group among these factors was difficult home conditions (4.5 per cent of the total series).

A larger proportion of the children kept in hospital for not purely medical therapy had been admitted for psychic diseases than of the children with no additional indications. The difference was highly significant ($\chi^2 = 13.58$, $p < 0.001$).

The percentages of admissions for functional symptoms did not differ significantly between these two groups. But in the group of children who had to wait for examination the percentage of functional symptoms (28.2 per cent) was relatively high. Table 38.

TABLE 40

IN THE ARENTS SEEK MEDICAL ADVICE IN TIME.

	Mental disorders	Functional symptoms	Other diseases	Total series
Admission in time	245 (3.4 %)*	567 (7.7 %)	6505 (88.9 %)	7317 (100.0 %)
Too late	14 (4.9 %)	13 (4.6 %) **	258 (90.5 %)	285 (100.0 %)
Total	259 (3.4 %)	580 (7.6 %)	6763 (89.0 %)	7602 (100.0 %)
			Not reported	352
				7954
			Non-response rate	4.4 %

higher than that of retarded admissions. The difference was highly significant ($\chi^2 = 198.69$ $p < 0.001$) Table 40

HOME NEGLECT

4.2 per cent of the present series of children were judged as neglected at home

Admissions for psychic diseases were more frequent among the neglected than the other children. The difference was highly significant ($\chi = 23.73$ $p < 0.001$)

Admissions for functional symptoms of the children neglected at home were less frequent than those of the other children The difference was almost significant (χ^2 4.06 $p < 0.05$) Table 41

PREVIOUS HOSPITAL ADMISSION OF CHILD FOR THE SAME DISEASE

29.1 per cent of the present series of children had been admitted previously for the same disease, while 70.9 per cent were admitted for the first time for their current disease.

The children who had previously been treated for the same disease were more numerous than those admitted for the first time, among the admissions for psychic diseases. The difference was almost significant ($\chi^2 = 4.39$ $p < 0.05$) Admissions for functional symptoms revealed no significant difference between frequencies of those who had been treated earlier for the same disease and the first admissions. Table 42

TABLE 41

WAS THE CHILD BEEN NEGLECTED AT HOME?

	Mental disorders	Functional symptoms	Other diseases	Total series
Yes	27 (8.6 %)	14 (4.5 %)	272 (86.9 %)	313 (100.0 %)
No	237 (3.3 %)	357 (7.7 %)*	6420 (89.0 %)	7214 (100.0 %)
Total	264 (3.5 %)	571 (7.6 %)	6692 (88.9 %)	7527 (100.0 %)
			Not reported	427
				7954
			Non-response rate	5.4 %

READINESS TO SEEK ADMISSION TO HOSPITAL

The purpose of the present investigation was also to find out the extent to which the readiness to seek hospital admission varied from family to family, and the social or socio-psychological background factors associated with such families

The factors chosen to illustrate this differing tolerance in the parents attitude to the child s illness and their seeking treatment at home or in hospital for the child were the following

- was the mother or the father opposed to the child s hospitalization,
- did the parents postpone bringing the child to hospital for economic reasons
- how long did the child suffer from this illness at home before admission to hospital
- had the child been previously hospitalized for the same disease
- had the father mother or the child s siblings been treated in hospital for disease.

WAS MOTHER OR FATHER OPPOSED TO HOSPITAL ADMISSION OF THE CHILD?

The study revealed that 0 48 per cent of the mothers and 0 75 per cent of the fathers resisted the child's admission to hospital The attitude of 3 5 per cent of the mothers and 10 6 per cent of the fathers was not known

DID THE PARENTS DELAY TAKING THE CHILD TO HOSPITAL FOR ECONOMIC REASONS?

Economic reasons had not delayed the child s hospital admission in 90 2 per cent of the cases The remaining 9 8 per cent of the parents had delayed taking the child to hospital because they feared the expense, or they could not say whether there had been any delay or the delay was for this reason

Children whose admission had been delayed for economic reasons were admitted for psychic diseases more frequently than those whose admission had not been delayed The difference was highly significant ($\chi^2 = 22\ 28$ $p < 0\ 001$)

In the functional symptoms group there was no difference between those whose admission had been delayed and those whose admission had not been delayed for economic reasons Table 39

TIMELINESS OF ADMISSION

In the hospital physician s opinion 96 3 per cent of the present series of children had been admitted in time and 3 7 per cent too late.

The percentage of retarded admissions was higher than that of timely admissions in the psychic diseases group The difference was highly significant ($\chi^2 = 65\ 20$ $p < 0\ 001$)

In the functional symptoms group the difference was the reverse the percentage of timely admissions (7 7 per cent) was

TABLE 39

DID PARENTS DELAY TAKING CHILD TO HOSPITAL FOR FEAR OF EXPENSE?

	Mental disorders	Functional symptoms	Other diseases	Total series
No	216 (3 0)	532 (7 5 %)	6379 (89.5 %)	7127 (100.0 %)
Yes	15 (8.7 %) } *	15 (8.7 %) }	142 (82.6 %)	172 (100.0 %)
Cannot say	34 (5.6 %) }	41 (6.8 %) }	529 (87 6 %)	604 (100.0 %)
Total	265 (3 4 %)	588 (7 4 %)	7050 (89.2 %)	7903 (100.0 %)
			Not reported	51
				7954
			Non-response rate	0 6 %

TABLE 40

DID THE ARE TS EEK MEDICAL ADVICE TIME?

	Mental disorders	Functional symptoms	Other diseases	Total series
Admission in time	245 (3.4 %)	567 (7.7 %)	6505 (88.9)	7317 (100.0 %)
Too late	14 (4.9 %)*	13 (4.6 %)	258 (90.5 %)	285 (100.0 %)
Total	259 (3.4)	580 (7.6 %)	6763 (89.0)	7602 (100.0 %)
			Not reported	352
				7954
			Non-response rate	4.4

higher than that of retarded admissions. The difference was highly significant ($\chi^2 = 198.69$ $p < 0.001$) Table 40

HOME NEGLECT

4.2 per cent of the present series of children were judged as neglected at home.

Admissions for *psychic diseases* were more frequent among the neglected than the other children. The difference was highly significant ($\chi^2 = 23.73$ $p < 0.001$)

Admissions for functional symptoms of *the children neglected at home were less* frequent than those of the other children. The difference was almost significant (χ^2 4.06, $p < 0.05$) Table *41*

PREVIOUS HOSPITAL ADMISSION OF CHILD FOR THE SAME DISEASE

29.1 per cent of the present series of children had been admitted previously for the same disease, while 70.9 per cent were admitted for the first time for their current disease.

The children who had previously been treated for the same *disease were more* numerous than those admitted for the first time, among the admissions for *psychic diseases. The difference was al*most significant ($\chi^2 = 4.39$ $p < 0.05$) Admissions for functional symptoms re*vealed no* significant difference between frequencies of those who had been treated earlier for the same disease and the first *admissions.* Table 42.

TABLE 41

HAD THE CHILD BEEN NEGLECTED AT HOME?

	Mental disorders	Functional symptoms	Other diseases	Total series
Yes	27 (8.6)	14 (4.5)	272 (86.9 %)	313 (100.0 %)
No	237 (3.3)	557 (7.7 %)	6420 (89.0 %)	7214 (100.0 %)
Total	264 (3.5)	571 (7.6)	6692 (88.9 %)	7527 (100.0)
			Not reported	427
				7954
			Non-response rate	5.4 %

READINESS TO SEEK ADMISSION TO HOSPITAL

The purpose of the present investigation was also to find out the extent to which the readiness to seek hospital admission varied from family to family and the social or socio-psychological background factors associated with such families

The factors chosen to illustrate this differing tolerance in the parents attitude to the child s illness and their seeking treatment at home or in hospital for the child were the following

— was the mother or the father opposed to the child s hospitalization,
— did the parents postpone bringing the child to hospital for economic reasons
  how long did the child suffer from this illness at home before admission to hospital,
— had the child been previously hospitalized for the same disease
— had the father mother or the child s siblings been treated in hospital for disease.

WAS MOTHER OR FATHER OPPOSED TO HOSPITAL ADMISSION OF THE CHILD?

The study revealed that 0 48 per cent of the mothers and 0 75 per cent of the fathers resisted the child's admission to hospital The attitude of 3 5 per cent of the mothers and 10 6 per cent of the fathers was not known

DID THE PARENTS DELAY TAKING THE CHILD TO HOSPITAL FOR ECONOMIC REASONS?

Economic reasons had not delayed the child s hospital admission in 90 2 per cent of the cases The remaining 9 8 per cent of the parents had delayed taking the child to hospital because they feared the expense or they could not say whether there had been any delay or the delay was for this reason

Children whose admission had been delayed for economic reasons were admitted for psychic diseases more frequently than those whose admission had not been delayed The difference was highly significant ($\chi^2 = 22\ 28$, $p < 0\ 001$)

In the functional symptoms group there was no difference between those whose admission had been delayed and those whose admission had not been delayed for economic reasons. Table 39

TIMELINESS OF ADMISSION

In the hospital physician s opinion 96 3 per cent of the present series of children had been admitted in time and 3 7 per cent too late.

The percentage of retarded admissions was higher than that of timely admissions in the psychic diseases group The difference was highly significant ($\chi^2 = 65\ 20$ $p < 0\ 001$)

In the functional symptoms group the difference was the reverse the percentage of timely admissions (7 7 per cent) was

TABLE 39

DID PARENTS DELAY TAKING CHILD TO HOSPITAL FOR FEAR O EXP CES?

	Mental disorders	Functional symptoms	Other diseases	Total series
No	216 (3 0 %)	532 (7 5 %)	6379 (89.5 %)	7127 (100.0 %)
Yes	15 (8.7 %)	15 (8.7 %)	142 (82.6)	172 (100.0 %)
Cannot say	34 (5 6 %) *	41 (6.8 %)	529 (87 6 %)	604 (100.0 %)
Total	265 (3.4 %)	588 (7 4 %)	7050 (89 2 %)	7903 (100.0 %)
			Not reported	51
				7954
			Non-response rate	0.6 %

Discussion

a) General discussion

Since the purpose was to study factors affecting hospital utilization, morbidity resulting in hospitalization had to be measured.

The present series did constitute a representative sample of what may be termed morbidity resulting in hospital admissions. As the social and psychological factors of the admitted patients and their families were analysed the factors which affect morbidity resulting in hospital admission were measured simultaneously

The present series consisted of patients hospitalized for treatment and warrants no conclusions on the general morbidity rate. Many patients stay at home, and many others are treated in outpatient clinics and by private practitioners.

It may be suggested that all cases beyond a certain degree of severity are treated in hospital. However the chances of hospital admission vary in different parts of Finland and it has been shown that distance from hospital plays part in seeking admission (103)

It was found, when the study was based on the hospital physicians opinion, that factors other than the purely medical formed a relatively small group The medical indications were responsible for 90 8 per cent of all admissions. One of the reasons is perhaps the shortage of beds in children s wards.

Is it desirable to admit a child to hospital for indications other than the purely medical There are two sides to this question the child s health is naturally of first importance But cognizant as we are of the heavy expenses the community incurs for hospital therapy it is worth pondering whether the children who have, for example, common colds and whose mothers are employed outside the home should not be provided with care and treatment without blocking a very necessary hospital bed with a child patient that could well be nursed at home by a home-help

If it is seen that the child s mental health is jeopardized unless the child is admitted to hospital for a period — say until another nursing place is provided — the child s interest must be given priority

b) Discussion of the results

Sex of the child

A study of the percentages previously published in the literature on the sex ratios reveals that boys are usually more numerous, while there are fluctuations depending on the group selected for study Table 43 quotes some percentages taken from the literature. MacDermott (1963) reported a difference in boy/girl ratios of child patients according to whether or not the parents were skilled workers. It was found that, in the skilled workers group, 74 per cent of the children were boys, while the percentage for the unskilled workers group was 70 In 1967 the same author found while studying psychotic children, that in the two highest social classes the boy/girl ratio showed a higher percentage of boys than in the lower social classes. Lowe (1966) on the other hand, found no statistically significant difference between girls and boys in his material of psychiatric childhood disorders, but when he studied the autistic group separately he found a boy/girl ratio of 2.8/1.0.

TABLE 42

HAD THE CHILD BEEN PREVIOUSLY HOSPITALIZED FOR THIS DISEASE?

	Mental disorders	Functional symptoms	Other diseases	Total series
Yes	88 (4 0 %)	162 (7 5 %)	1922 (88.5 %)	2172 (100 0 %)
No	162 (3 1 %)	390 (7 4)	4744 (89.5 %)	5296 (100.0 %)
Total	250 (3.3 %)	552 (7 4 %)	6666 (89.5 %)	7468 (100.0 %)
			Not reported	486
				7954
			Non-response rate	6 1 %

PREVIOUS HOSPITAL ADMISSION OF MOTHER

51 5 per cent of the mothers of the present series of children had been treated in hospital (excluding parturitions)

A comparison between the children of the mothers treated in hospital with those who had not been in hospital revealed no significant differences in the frequencies of either psychic diseases or functional symptoms as principal diagnoses

PREVIOUS HOSPITAL ADMISSION OF FATHER

51 5 per cent of the fathers of the present series of children had been hospitalized at some time during their lives

The frequencies of mental disorders and functional symptoms as principal diagnosis did not differ significantly between children of unhospitalized and hospitalized fathers

PREVIOUS HOSPITAL ADMISSION OF THE CHILD S SIBLINGS

36 2 per cent of the present series of children had a sibling who had been in hospital 28 8 per cent either had no siblings or their admissions were not known while 35 0 per cent had siblings but none of them had been hospitalized

For the statistical test the child patients were divided into those whose sibling had been in hospital and others The differences between these groups in the frequency of admissions for psychic diseases or functional symptoms were not significant

Discussion

a) General discussion

Since the purpose was to study factors affecting hospital utilization, morbidity resulting in hospitalization had to be measured.

The present series did constitute a representative sample of what may be termed morbidity resulting in hospital admissions. As the social and psychological factors of the admitted patients and their families were analysed, the factors which affect morbidity resulting in hospital admission were measured simultaneously.

The present series consisted of patients hospitalized for treatment and warrants no conclusions on the general morbidity rate. Many patients stay at home, and many others are treated in outpatient clinics and by private practitioners.

It may be suggested that all cases beyond a certain degree of severity are treated in hospital. However the chances of hospital admission vary in different parts of Finland and it has been shown that distance from hospital plays part in seeking admission (103).

It was found, when the study was based on the hospital physicians opinion, that factors other than the purely medical formed a relatively small group. The medical indications were responsible for 90.8 per cent of all admissions. One of the reasons is perhaps the shortage of beds in children's wards.

Is it desirable to admit a child to hospital for indications other than the purely medical? There are two sides to this question: the child's health is naturally of first importance. But cognizant as we are of the heavy expenses the community incurs for hospital therapy, it is worth pondering whether the children who have, for example, common colds and whose mothers are employed outside the home should not be provided with care and treatment without blocking a very necessary hospital bed with a child patient that could well be nursed at home by a home-help.

If it is seen that the child's mental health is jeopardized unless the child is admitted to hospital for a period — say until another nursing place is provided — the child's interest must be given priority.

b) Discussion of the results

Sex of the child

A study of the percentages previously published in the literature on the sex ratios reveals that boys are usually more numerous, while there are fluctuations depending on the group selected for study. Table 43 quotes some percentages taken from the literature. MacDermott (1965) reported a difference in boy/girl ratios of child patients according to whether or not the parents were skilled workers. It was found that, in the skilled workers group, 74 per cent of the children were boys, while the percentage for the unskilled workers group was 70. In 1967 the same author found, while studying psychotic children, that in the two highest social classes the boy/girl ratio showed a higher percentage of boys than in the lower social classes. Lowe (1966) on the other hand, found no statistically significant difference *between girls* and boys in his material of psychiatric childhood disorders, but when he studied the autistic group separately he found a boy/girl ratio of 2.8/1.0.

TABLE 13

SEX RATIO IN THE CHILD—PSYCHIATRIC SERIES DESCRIBED EARLIER IN THE LITERATURE

Author	Year	Diagnosis group	Boys Number	%	Girls Number	%
Hallgren	1956	Enuresis	100	68.5	46	31.5
Bender	1956	Schizophrenia	95	67 0	47	33.0
Phillips	1957	Autistic children	23	85 0	4	15 0
Inglis et al	1958	Child—psychiatric patients	77	54 0	66	46.0
Ekström et al	1961	Nervous abdominal pain	146	48 7	154	51 3
Hunt	1961	Child guidance clinic patients	398	67 0	193	33.0
Valanne	1961	Child—psychiatric patients	271	56 0	213	44 0

Hunt (1961) from his study of child guidance clinic material, found that boys were heavily over represented Looking for a reason he came to the conclusion that general behaviour and role expectations vis-à vis sons tend to reduce parental tolerance limits

In the present series of mental disorders there were also more boys than girls The ratio was 2/1 The reason for this can be that boys with mental disorders behave in a wilder fashion and therefore cause more stress to the environment than girls This may be one reason why the physician is approached more readily when a boy is concerned

It may also be claimed in view of psychiatric diseases that boys are more susceptible to psychic damage A certain degree of complaining and hypochondria in boys may also be the cause of treatment being sought sooner for them

It is also possible that boys are generally affected by diseases more often than girls. Some examples from Finland a study of deaths under the age of one year in 1963 revealed that 837 boys and 659 girls died For 1964 the figures were 815 boys and 554 girls (94) Bardy (1966) found that 105 boys per 100 girls died at an age under 14 days Comparing the sex ratios among the mentally subnormal in Finland Amnell et al. (1965) found that of the 4000 patients examined 3 07 per thousand were men and 2 94 per thousand were women There were statistically significantly more men than women among the idiots

Age of the child

In the present study there were significantly more children between 7 and 15 years than children of other age groups in both mental disorders and functional symptoms groups The reason for this phenomen may be that mental disorders and many psychosomatic symptoms are more frequent in teenagers (22 66)

Illegitimacy of the child

In the present study there were more social indications for illegitimate than legitimate children The reason for this may be that the unmarried mothers must be employed outside the home without other facilities than the hospital when the child falls ill The unmarried mothers may also be uncertain and lacking in spiritual support from their environment. Most single mothers live in poorer economic conditions than married women (10) Paavola (1967) also showed that these unmarried women were often employed in heavy manual work.

The situation of unmarried women is not always so difficult. The community helps them in several ways. They have, for example priority for day nurseries and kindergartens. Berfenstam and Wilner (1966) showed in their work about Swedish unmarried women that young mothers with one child often got help from their parents and that these unmarried women had managed much better than they had dared to expect at the outset.

Seniority of the child among siblings

The only child was seldom brought to hospital for mental disorders. The reason may be that parents do not see, or refuse to see, the psychic disorder. Other possible reasons may be that the mother has more time to care for the child at home or that she does not let other people see her deficient only child. The only child, furthermore, is often the first child of a young family — so young that the mental disorders have not yet emerged. The parents may also consult an experienced private physician in good time and visit the outpatient department.

The reason why the only child is brought to hospital for functional symptoms more often than the average, is perhaps the very fact that it is the first child of a young couple, and all symptoms are given exceptional attention. Parental uncertainty may be reflected in the fact that they approach a physician more readily and wish their child to be examined at hospital.

When the number of children increases, the tendency to bring a child to hospital for psychic disorders seems to grow slightly. The reason may be that in these families the children approach the age at which mental disorders break out, or that the parents are freer in their attitude to psychic symptoms.

Dvoretsky (1966) presented a review of the literature on the psychic importance of seniority among siblings to the individual. From his review the author came to the conclusion that seniority among siblings is not a separate and unambiguous variable and that it should be considered in relation to other factors.

Importance of the mother

Both Spence and co-workers (88) and Straus and co-workers (92) showed that there was a definite relationship between child's admission to hospital and maternal capacity for home care.

In the present series there were more social indications when the mother was sick or in poor condition than when she was healthy. If the mother was full-time employed there were also more additional social indications than if she was at home. These results agree with those of Spence and Straus.

The fact that in the present series there were more mental disorders in children who had only a father than in those who had both parents, also indicates the importance of the mother. The result also agrees with Annell's opinion (6) that living without the mother may cause psychic disturbances in children.

One reason for over representation of lonely fathers' children may also be the fact pointed out by Chaskel (12) that the solitary fathers are nowadays more integrated into the framework of social welfare.

Parents' ownership of a private car

In the families with a private car the psychological factors seemed to have some influence on the hospital admission of children. In the families with no private car there were more frequently additional social indications. In order to measure if the ownership of a private car was a sign of wealth in the present series, the car ownership and income of parents were correlated. The phi-coefficient was 0.284. This showed that between these factors there was only a moderate correlation.

From the practical point of view ownership of a car makes it easier to bring the diseased child to a physician's consulting room and to hospital. Both Haavio-Mannila (26) and Väänänen (103) showed that when the distance from home to hospital was long the children were not so readily taken to hospital.

From the beginning of the year 1964 general health insurance was established in Finland and the people were given economic help for journeys to hospital and to physicians. Now it is easier to take a taxi or an ambulance when there is no fear of economic strains because of the journeys.

Ownership of a television set at home

On Finnish Television there is a programme »The TV home doctor» primarily on children's diseases, which was seen

TABLE 13

SEX RATIO IN THE CHILD—PSYCHIATRIC SERIES DESCRIBED EARLIER IN THE LITERATURE

Author	Year	Diagnosis group	Boys Number	Boys %	Girls Number	Girls %
Hallgren	1956	Enuresis	100	68.5	46	31.5
Bender	1956	Schizophrenia	95	67.0	47	33.0
Phillips	1957	Autistic children	23	85.0	4	15.0
Inglis et al.	1958	Child—psychiatric patients	77	54.0	66	46.0
Ekström et al.	1961	Nervous abdominal pain	146	18.7	154	51.3
Hunt	1961	Child guidance clinic patients	398	67.0	193	33.0
Valanne	1961	Child—psychiatric patients	271	56.0	213	44.0

Hunt (1961) from his study of child guidance clinic material, found that boys were heavily over represented. Looking for a reason he came to the conclusion that general behaviour and role expectations vis-à-vis sons tend to reduce parental tolerance limits.

In the present series of mental disorders there were also more boys than girls. The ratio was 2/1. The reason for this can be that boys with mental disorders behave in a wilder fashion and therefore cause more stress to the environment than girls. This may be one reason why the physician is approached more readily when a boy is concerned.

It may also be claimed in view of psychiatric diseases that boys are more susceptible to psychic damage. A certain degree of complaining and hypochondria in boys may also be the cause of treatment being sought sooner for them.

It is also possible that boys are generally affected by diseases more often than girls. Some examples from Finland: a study of deaths under the age of one year in 1963 revealed that 837 boys and 659 girls died. For 1964 the figures were 815 boys and 554 girls (94). Bardy (1966) found that 105 boys per 100 girls died at an age under 14 days. Comparing the sex ratios among the mentally subnormal in Finland Åmnell et al (1965) found that of the 4000 patients examined 3.07 per thousand were men and 2.94 per thousand were women. There were statistically significantly more men than women among the idiots.

Age of the child

In the present study there were significantly more children between 7 and 15 years than children of other age groups in both mental disorders and functional symptoms groups. The reason for this phenomenon may be that mental disorders and many psychosomatic symptoms are more frequent in teenagers (22, 66).

Illegitimacy of the child

In the present study there were more social indications for illegitimate than legitimate children. The reason for this may be that the unmarried mothers must be employed outside the home without other facilities than the hospital when the child falls ill. The unmarried mothers may also be uncertain and lacking in spiritual support from their environment. Most single mothers live in poorer economic conditions than married women (10). Paavola (1967) also showed that these unmarried women were often employed in heavy manual work.

The situation of unmarried women is not always so difficult. The community helps them in several ways. They have, for example, priority for day nurseries and kindergartens. Berfenstam and Wilner (1966) showed in their work about Swedish unmarried women that young mothers with one child often got help from their parents and that these unmarried women had managed much better than they had dared to expect at the outset.

Seniority of the child among siblings

The only child was seldom brought to hospital for mental disorders. The reason may be that parents do not see, or refuse to see, the psychic disorder. Other possible reasons may be that the mother has more time to care for the child at home or that she does not let other people see her deficient only child. The only child, furthermore, is often the first child of a young family — so young that the mental disorders have not yet emerged. The parents may also consult an experienced private physician in good time and visit the outpatient department.

The reason why the only child is brought to hospital for functional symptoms more often than the average, is perhaps the very fact that it is the first child of a young couple, and all symptoms are given exceptional attention. Parental uncertainty may be reflected in the fact that they approach a physician more readily and wish their child to be examined at hospital.

When the number of children increases, the tendency to bring a child to hospital for psychic disorders seems to grow slightly. The reason may be that in these families the children approach the age at which mental disorders break out, or that the parents are freer in their attitude to psychic symptoms.

Dvoredsky (1966) presented a review of the literature on the psychic importance of seniority among siblings to the individual. From his review the author came to the conclusion that seniority among siblings is not a separate and unambiguous variable, and that it should be considered in relation to other factors.

Importance of the mother

Both Spence and co-workers (88) and Straus and co-workers (92) showed that there was definite relationship between child's admission to hospital and maternal capacity for home care.

In the present series there were more social indications when the mother was sick or in poor condition than when she was healthy. If the mother was full-time employed there were also more additional social indications than if she was at home. These results agree with those of Spence and Straus.

The fact that in the present series there were more mental disorders in children who had only a father than in those who had both parents, also indicates the importance of the mother. The result also agrees with Annell's opinion (6) that living without the mother may cause psychic disturbances in children.

One reason for over-representation of lonely fathers children may also be the fact pointed out by Chaskel (12) that the solitary fathers are nowadays more integrated into the framework of social welfare.

Parents ownership of a private car

In the families with a private car the psychological factors seemed to have some influence on the hospital admission of children. In the families with no private car there were more frequently additional social indications. In order to measure, if the ownership of a private car was a sign of wealth in the present series, the car ownership and income of parents were correlated. The phi-coefficient was 0.284. This showed that between these factors there was only a moderate correlation.

From the practical point of view ownership of a car makes it easier to bring the diseased child to a physician's consulting room and to hospital. Both Haavio-Mannila (26) and Väänänen (103) showed that when the distance from home to hospital was long the children were not so readily taken to hospital.

From the beginning of the year 1964 general health insurance was established in Finland and the people were given economic help for journeys to hospital and to physicians. Now it is easier to take a taxi or an ambulance, when there is no fear of economic strains because of the journeys.

Ownership of a television set at home

On Finnish Television there is a programme »The TV home doctor» primarily on children's diseases, which was seen

in 1963 by an average of 451 000 viewers (34) This kind of programme can make parents pay more attention to their children's health and possible symptoms of diseases Thus the parents bring their child earlier to the physician and to hospital when the disease is not yet so bad

On the other hand there may be negative effects on the parental mind creation of futile anxiety by programmes dealing with diseases. Over protective parents can therefore be provoked into unnecessary visits to a doctor The fact that in the present series there were more admissions for functional symptoms from families with a TV set than from homes with no TV set may partly reflect this mechanism Also the fact that there were more additional psychological indications in the TV-owners than in others may reflect parental anxiety over protection and fear

The ownership of a TV set was considered as a socio-psychological factor In Finland in 1963 the so called intellectual workers were over represented as TV owners (34) Himmelweit et al (1958) studied the differences between TV viewers and non viewers and they came to the conclusion that TV could not abolish the pre-existing differences which were apparently due to social class

Urban and rural children

Social and psychological indications were more frequent for urban than for rural children In Helsinki there were more social indications than in other communities This may reflect the difficulties of home care in cities and also the accumulating social difficulties in big cities The result from Helsinki agrees with the results from Paris (92)

In the mental disorders group there were no differences between urban and rural children One might have expected that there would be more psychiatric problems among urban than rural children as pointed out by Miller (66) The fact that the present study deals with hospital patients may obscure the real differences.

Distance from the child's home to nearest physician or hospital

The distance between home and the nearest physician played no part, according to the present material when the child was affected with psychic diseases or functional symptoms But the distance to hospital was a factor correlated with the child's admission for the above diseases or symptoms. When psychic diseases were in question the child was even taken to a distant hospital The fact that distance between the hospital and the home of patients with psychic diseases was very great suggests that the hospitals treating these cases should be more evenly distributed The preponderance of the children brought for treatment over long distances is perhaps explained by the fact that the material includes the psychiatric wards of the Children's Hospital University of Helsinki the City Hospital of Helsinki and the Children's Castle in Helsinki which admit patients from all over Finland During the year studied no child psychiatrists were available in hospitals in Finland except in Helsinki and Turku

A hospital catering for special patients attracts relatively more of its patients from the immediate area than from more outlying districts. The cases admitted e.g for psychiatric diseases from North Finland to South Finland hospitals may have been more severe than the cases coming from the more immediate area

The cerebral palsy children with motor defects, classified under the mental disorders group in the present material form a special category gathered from all over Finland to the Children's Castle in Helsinki. Not until 1966 could special treatment for children with motor defects be had in North Finland The Pediatric Department of the University of Oulu founded in 1964 started this work in 1966

South and North Finland

While discussing the difference between South and North Finland the work of Christensen (1956) in Denmark should be remembered He studied admissions to hospital from two types of districts, a good and a bad in the social sense of the word

He found that admissions from the poor social areas were twice as frequent as from the better areas. The difference was mainly due to admissions of children under one year of age. Some diseases, such as scarlet fever tuberculosis and oligophrenia, were equally represented, while others, such as infections of the upper respiratory tract, anaemia and prematurity showed twice this rate of representation. The general finding was that the incidence of infections was three to four times higher in the poor than in the good housing districts.

Haavio-Mannila (1962) found that a remote place of residence did not affect the incidence of diseases, whereas consultation for treatment and location of residence were correlated. The incidence of diseases was highest in all age groups in the northern parts of the country

The division of the country into North and South Finland was based on differences in the number of hospital beds and physicians per inhabitants. In Lapland the northernmost part of the country there are relatively more hospital beds for children (= Children's Hospital, Rovaniemi) than in the other parts of North Finland. In Lapland, however there are very long distances and the roads are sometimes much more difficult to drive than in South Finland. Väänänen (103) showed that the distances played significant part in the hospital admissions of children in Lapland He also showed that, for example, the distance from home to nearest highway had some influence

In South Finland there were more psychological and particularly social indications than in North Finland. The same indications were more frequent in cities. It may be that behind this result there are special social factors in South Finland and in cities more crowded dwellings, more employed mothers, and so on

Hospital type

The higher incidence of psychological factors in university teaching hospitals and in the Children's Castle, Helsinki, may be due to the greater interest the personnel of these hospitals takes in these factors, but it may even be that patients with additional psychological indications are more easily admitted to this hospital type with special child psychiatric personnel.

A typical city hospital, the City Hospital of Helsinki, is exceptional in that the social indications were more frequent there than elsewhere Two investigations (Rantasalo 1955 Väänänen 1962) had been carried out at this hospital before and the personnel was well adapted to record the additional social factors in hospital admissions. This may be a contributory factor yet it seems evident that since this hospital gathers its patients from the Helsinki city area with the many difficulties encountered in providing care for the children at home, the social indications were of greater importance for children's admission than in other hospitals. Sociological differences might also affect the result in Helsinki the help and care of minor illnesses in the family by grandparents, relatives and neighbours are obviously less available than in the less changeable countryside or small-town societies.

The hospitals with one pediatrician form the group of children's hospitals in which additional social factors played a great part for the child's admission. The reason for this may be that the rural district surrounding these hospitals is mostly both medically and socially underdeveloped.

Most mental disorders were treated in university hospitals and in the Children's Castle, Helsinki. Hospitals with several pediatricians came next and only very few patients with mental disorders were treated in the City Hospital of Helsinki and in hospitals with one pediatrician. Especially in the units with one pediatrician there may even be great difficulties in treating patients with mental disorders since there are so many acute diseases and so few specially trained personnel.

There can also be some pressure on pediatric wards (by mentally subnormal children) because of the lack of beds in the institutions for the mentally handicapped. In his study of the mentally subnormal in Finland in 1966 Tarvainen (96) came to the conclusion that 10,200

in 1963 by an average of 451 000 viewers (34) This kind of programme can make parents pay more attention to their children's health and possible symptoms of diseases Thus the parents bring their child earlier to the physician and to hospital when the disease is not yet so bad

On the other hand there may be negative effects on the parental mind creation of futile anxiety by programmes dealing with diseases Over protective parents can therefore be provoked into unnecessary visits to a doctor The fact that in the present series there were more admissions for functional symptoms from families with a TV set than from homes with no TV set may partly reflect this mechanism Also the fact that there were more additional psychological indications in the TV-owners than in others may reflect parental anxiety over protection and fear

The ownership of a TV set was considered as a socio-psychological factor In Finland in 1963 the so called intellectual workers were over represented as TV owners (34) Himmelweit et al (1958) studied the differences between TV viewers and non viewers and they came to the conclusion that TV could not abolish the pre-existing differences which were apparently due to social class.

Urban and rural children

Social and psychological indications were more frequent for urban than for rural children In Helsinki there were more social indications than in other communities This may reflect the difficulties of home care in cities and also the accumulating social difficulties in big cities The result from Helsinki agrees with the results from Paris (92)

In the mental disorders group there were no differences between urban and rural children One might have expected that there would be more psychiatric problems among urban than rural children as pointed out by Miller (66) The fact that the present study deals with hospital patients may obscure the real differences.

Distance from the child's home to nearest physician or hospital

The distance between home and the nearest physician played no part, according to the present material, when the child was affected with psychic diseases or functional symptoms But the distance to hospital was a factor correlated with the child's admission for the above diseases or symptoms. When psychic diseases were in question, the child was even taken to a distant hospital The fact that distance between the hospital and the home of patients with psychic diseases was very great suggests that the hospitals treating these cases should be more evenly distributed The preponderance of the children brought for treatment over long distances is perhaps explained by the fact that the material includes the psychiatric wards of the Children's Hospital, University of Helsinki the City Hospital of Helsinki and the Children's Castle in Helsinki which admit patients from all over Finland During the year studied no child psychiatrists were available in hospitals in Finland except in Helsinki and Turku.

A hospital catering for special patients attracts relatively more of its patients from the immediate area than from more outlying districts. The cases admitted e.g for psychiatric diseases from North Finland to South Finland hospitals may have been more severe than the cases coming from the more immediate area

The cerebral palsy children with motor defects, classified under the mental disorders group in the present material form a special category gathered from all over Finland to the Children's Castle in Helsinki Not until 1966 could special treatment for children with motor defects be had in North Finland The Pediatric Department of the University of Oulu founded in 1964 started this work in 1966

South and North Finland

While discussing the difference between South and North Finland the work of Christensen (1956) in Denmark should be remembered He studied admissions to hospital from two types of districts, a good and a bad in the social sense of the word

He found that admissions from the poor social areas were twice as frequent as from the better areas. The difference was mainly due to admissions of children under one year of age. Some diseases, such as scarlet fever tuberculosis and oligophrenia, were equally represented, while others, such as infections of the upper respiratory tract, anaemia and prematurity showed twice this rate of representation. The general finding was that the incidence of infections was three to four times higher in the poor than in the good housing districts.

Haavio-Mannila (1962) found that a remote place of residence did not affect the incidence of diseases, whereas consultation for treatment and location of residence were correlated. The incidence of diseases was highest in all age groups in the northern parts of the country

The division of the country into North and South Finland was based on differences in the number of hospital beds and physicians per inhabitants. In Lapland, the northernmost part of the country there are relatively more hospital beds for children (= Children's Hospital Rovaniemi) than in the other parts of North Finland. In Lapland, however there are very long distances and the roads are sometimes much more difficult to drive than in South Finland. Väänänen (103) showed that the distances played significant part in the hospital admissions of children in Lapland He also showed that, for example, the distance from home to nearest highway had some influence

In South Finland there were more psychological and particularly social indications than in North Finland The same indications were more frequent in cities. It may be that behind this result there are special social factors in South Finland and in cities more crowded dwellings, more employed mothers and so on

Hospital type

The higher incidence of psychological factors in university teaching hospitals and in the Children's Castle, Helsinki, may be due to the greater interest the personnel of these hospitals takes in these factors, but it may even be that patients with additional psychological indications are more easily admitted to this hospital type with special child psychiatric personnel.

A typical city hospital, the City Hospital of Helsinki, is exceptional in that the social indications were more frequent there than elsewhere. Two investigations (Rantasalo 1955 Väänänen 1962) had been carried out at this hospital before and the personnel was well adapted to record the additional social factors in hospital admissions. This may be a contributory factor yet it seems evident that since this hospital gathers its patients from the Helsinki city area with the many difficulties encountered in providing care for the children at home, the social indications were of greater importance for children's admission than in other hospitals. Sociological differences might also affect the result in Helsinki the help and care of minor illnesses in the family by grandparents, relatives and neighbours are obviously less available than in the less changeable countryside or small-town societies.

The hospitals with one pediatrician form the group of children's hospitals in which additional social factors played a great part for the child's admission The reason for this may be that the rural district surrounding these hospitals is mostly both medically and socially underdeveloped.

Most mental disorders were treated in university hospitals and in the Children's Castle, Helsinki. Hospitals with several pediatricians came next and only very few patients with mental disorders were treated in the City Hospital of Helsinki and in hospitals with one pediatrician. Especially in the units with one pediatrician there may even be great difficulties in treating patients with mental disorders since there are so many acute diseases and so few specially trained personnel.

There can also be some pressure on pediatric wards (by mentally subnormal children) because of the lack of beds in the institutions for the mentally handicapped. In his study of the mentally subnormal in Finland in 1966 Tarvainen (96) came to the conclusion that 10 200

beds for these patients were required in Finland The number of beds in institutions was in June 1964 about 2300

Thus some children who must be cared for at home due to lack of beds in the institutions may sometimes be admitted to pediatric wards — not for purely medical reasons but because of some kind of family exhaustion

Length of hospital stay

As far as is known the length of hospital stay and social conditions of mentally disturbed children have not been studied previously The studies of adult psychiatric patients were reviewed by Vornbrock and Wences (1967) In their own study the authors found that the age of patients rather than education or occupational status was the significant factor in relation to length of hospital stay

In the present study delays in discharge from hospital were frequent in both mental disorders and functional symptoms. In both diagnostic groups the most important reason was the waiting for examinations In mental disorders this group was 6 8 % and in functional symptoms 28 2 / Certain home conditions and distance from hospital to home also contributed to the overlong stay in hospital Finland may therefore need more examination facilities and disintegration of hospitals for mental disorders in children

Parental readiness to seek admission for their child

The parental attitude to hospital admission of their child was generally favourable. Only less than one per cent of parents opposed the admission If the mental disorders and functional symptoms groups are taken together only 13 fathers and 7 mothers were in opposition to the admission

Two factors which probably influenced this result were the shortage of hospital beds and the fact that hospital treatment is relatively inexpensive in Finland The patient or the parents of the patient pay only 10—20 per cent of all hospital charges and the community pays the rest A hospital day costs in Finland 6 Fmk (equivalent to 1 86 U S $)

Straus et al (92) emphasized that there are factors in certain families which can lead to high incidence of hospital admission of family members In these cases the purely medical indications for admission are too slight. The same child can also be admitted several times for the same disease and on too slight medical basis.

In the present study there was a high incidence of delays for economic reasons of admissions too late, of home neglect of the child and of previous admissions of the child in the mental disorders group This all shows that this diagnosis group has numerous special problems.

The incidence of hospital admissions of other family members was low which may mean that the readiness to seek hospital admission was in the present study more connected with the child and its disease than with some general factor in the family

Summary

A study of the social and psychological factors in hospital admission of children was made in Finland 1963—64. During four months (April, May and August 1963 and January 1964) a comprehensive questionnaire with 70 questions was completed for all children admitted to 21 children's hospitals. Only 2 children's hospitals in the whole country could not participate in the study. The questions investigated the socio-economic and socio-psychological factors in the family, the child's diseases and parental attitudes towards child, hospital and disease. The study comprised altogether 7954 children.

In the present study the collected data were analysed by computer to find those additional social and psychological factors which affect hospital admission of children. Two diagnosis groups were also analysed more closely for social and socio-psychological background factors: mental disorders and so called functional symptoms in the childhood.

I SOCIAL AND PSYCHOLOGICAL FACTORS INFLUENCING HOSPITAL ADMISSION

In the total series of patients there were more boys than in the total Finnish population when both sexes were divided in different age groups.

Social indications in the hospital admission were more frequent for illegitimate than legitimate children, and also more frequent when the only child was involved than when the child was one of several siblings. Additional social factors contributed to hospital admission more often when the mother was sick or in poor condition than if she was healthy.

Psychological factors in the family were more frequent in the higher income bracket than in the lower one. Social factors were more frequent in the lower income bracket than in the higher one. Social factors influenced hospital admission of farmers' children less frequently than non-farmers.

If the family had a private car there were more frequently additional psychological factors than in those families which had no private car. There were more social factors in those families which did not have a car than in those which did.

Ownership of a TV set was considered as a socio-psychological factor. When the family had a TV set there were more frequently additional psychological factors than when the family had no TV set.

Social and psychological factors were more frequent for urban than for rural children. When Helsinki, a small metropolis, was tested against all other community types, it was found that there were more social indications for Helsinki children than for children from other communities.

To study the influence of public health resources the country was divided into two parts. The part with fewer physicians and fewer hospital beds was named North Finland and the second part South Finland. Both social and psychological indications were more frequent in South Finland than in North Finland.

The 21 participating hospitals were divided into four groups according to their working facilities. Psychological indications were more frequent in the university hospital and in a special pediatric hospital in Helsinki, named Childrens Castle, than in other hospital types. Social indications were more frequent in the City Hospital of Helsinki and in the hospitals with only one pediatrician than in other hospital types.

beds for these patients were required in Finland The number of beds in institutions was in June 1964 about 2300

Thus some children who must be cared for at home due to lack of beds in the institutions, may sometimes be admitted to pediatric wards — not for purely medical reasons but because of some kind of family exhaustion

Length of hospital stay

As far as is known the length of hospital stay and social conditions of mentally disturbed children have not been studied previously The studies of adult psychiatric patients were reviewed by Vornbrock and Wences (1967) In their own study the authors found that the age of patients rather than education or occupational status was the significant factor in relation to length of hospital stay

In the present study delays in discharge from hospital were frequent in both mental disorders and functional symptoms. In both diagnostic groups the most important reason was the waiting for examinations. In mental disorders this group was 6 8 % and in functional symptoms 28.2 % Certain home conditions and distance from hospital to home also contributed to the overlong stay in hospital Finland may therefore need more examination facilities and disintegration of hospitals for mental disorders in children

Parental readiness to seek admission for their child

The parental attitude to hospital admission of their child was generally favourable. Only less than one per cent of parents opposed the admission If the mental disorders and functional symptoms groups are taken together only 13 fathers and 7 mothers were in opposition to the admission

Two factors which probably influenced this result were the shortage of hospital beds and the fact that hospital treatment is relatively inexpensive in Finland The patient or the parents of the patient pay only 10—20 per cent of all hospital charges and the community pays the rest A hospital day costs in Finland 6 Fmk (equivalent to 1 86 U S $)

Straus et al (92) emphasized that there are factors in certain families which can lead to high incidence of hospital admission of family members In these cases the purely medical indications for admission are too slight The same child can also be admitted several times for the same disease and on too slight medicalbasis.

In the present study there was a high incidence of delays for economic reasons, of admissions too late, of home neglect of the child and of previous admissions of the child in the mental disorders group This all shows that this diagnosis group has numerous special problems

The incidence of hospital admissions of other family members was low which may mean that the readiness to seek hospital admission was in the present study more connected with the child and its disease than with some general factor in the family

Summary

A study of the social and psychological factors in hospital admission of children was made in Finland 1963—64. During four months (April, May and August 1963 and January 1964) a comprehensive questionnaire with 70 questions was completed for all children admitted to 21 children's hospitals. Only 2 children's hospitals in the whole country could not participate in the study. The questions investigated the socio-economic and socio-psychological factors in the family, the child's diseases and parental attitudes towards child, hospital and disease. The study comprised altogether 7954 children.

In the present study the collected data were analysed by computer to find those additional social and psychological factors which affect hospital admission of children. Two diagnosis groups were also analysed more closely for social and socio-psychological background factors: mental disorders and so called functional symptoms in the childhood.

I SOCIAL AND PSYCHOLOGICAL FACTORS INFLUENCING HOSPITAL ADMISSION

In the total series of patients there were more boys than in the total Finnish population when both sexes were divided in different age groups.

Social indications in the hospital admission were more frequent for illegitimate than legitimate children, and also more frequent when the only child was involved than when the child was one of several siblings. Additional social factors contributed to hospital admission more often when the mother was sick or in poor condition than if she was healthy.

Psychological factors in the family were more frequent in the higher income bracket than in the lower one. Social factors were more frequent in the lower income bracket than in the higher one. Social factors influenced *hospital admission* of farmers' children less frequently than non-farmers.

If the family had a private car there were more frequently additional psychological factors than in those families which had no private car. There were more social factors in those families which did not have a car than in those which did.

Ownership of a TV set was considered as a socio-psychological factor. When the family had a TV set there were more frequently additional psychological factors than when the family had no TV set.

Social and psychological factors were more frequent for urban than for rural children. When Helsinki, a small metropolis, was tested against all other community types, it was found that there were more social indications for Helsinki children than for children from other communities.

To study the influence of public health resources the country was divided into two parts. The part with fewer physicians and fewer hospital beds was named North Finland and the second part South Finland. Both social and psychological *indications* were more frequent in South Finland than in North Finland.

The 21 participating hospitals were divided into four groups according to their working facilities. Psychological indications were more frequent in the university hospital and in a special pediatric hospital in Helsinki, named Childrens Castle, than in other hospital types. *Social indications* were more frequent in the City Hospital of Helsinki and in the hospitals with only one pediatrician than in other hospital types.

4

II SOCIO-ECONOMIC AND SOCIO-PSYCHOLOGICAL FACTORS IN MENTAL DISORDERS AND FUNCTIONAL SYMPTOMS

In both groups there were more frequently additional social and psychological factors in the hospital admission than admissions for purely medical indications

In the diagnosis group of mental disorders there were more boys than girls more children of 7—15 years of age than younger and more eldest children than others There were also more children of unmarried than married fathers and more children of fathers possessing a university degree than with lower educational level

In this diagnosis group there were more children from upper than from lower income families more children from such families which had a TV set than from families with no TV The same difference as in the ownership of a TV set was true of the ownership of a summer cottage The children had more frequently a distance from home to hospital exceeding 100 km than maximum 100 km

In mental disorders group children had to wait for admission more often and for a longer time than in other diseases. There were often factors which delayed the discharge of the child from hospital Parents had often delayed hospital admission for economic reasons The child was taken to hospital more often too late than in time and the home care of the child was frequently neglected The children had already been in hospital more frequently than admitted for the first time for this disease

In the diagnosis group of functional symptoms there were less children under one year than one year and older There were more children between 7—15 years of age than under 7 years The only child was admitted less frequently for functional symptoms than other children The group contained more children from families with one inhabitant per room than children from families with more than one inhabitant per room Children with a TV set at home were admitted more frequently than those who had no TV set at home The ownership of a summer cottage had the same influence.

The group contained a larger number of children living at a distance of more than 100 km from hospital than children with a maximum distance of 100 km between home and hospital more children from Helsinki than from other communities and more children from North Finland than from South Finland

In hospitals with one pediatrician there were less children with functional symptoms than in other hospital types

The children had to wait less frequently for more than one month than for a maximum of one month and admissions in time were more frequent than retarded admissions Admissions of children whose care was neglected at home were less frequent than admissions of other children

Acknowledgements

The subject for this study was suggested by my chief, Professor Ole Wasz Höckert, M.D. Head of the Department of Pediatrics University of Oulu During the course of the work he has advised and encouraged me, for which I am extremely grateful.

Professor Niilo Hallman M.D., Head of the Children's Hospital, University of Helsinki has given me practical guidance and constructive and valuable criticism of the study at all stages. My respectful thanks are due to him for his help

The biostatistics involved, ever since the collection of data was planned, were hand led by Timo Partanen, M.Sc., of the Institute of Occupational Health, Helsinki. He spared no effort to help me in the various statistical problems. Mathematical expertise has also been offered to me by Pertti Hyyrynen, M.Sc., of the Department of Mathematics, and the Computer Centre of the University of Oulu, and I owe a debt of gratitude to them both.

Since my study also concerned aspects of child-psychiatry I sought advice from Eero Valanne, M.D., Child Psychiatrist of the Children's Hospital, University of Helsinki. I am greatly indebted to him for encouragement and support.

Associated Professor Kauko Kouvalainen M.D., of the Pediatric Clinics, University of Turku has helped me with critical advice in his capacity of faculty expert, for which I am very grateful.

Acting Professor Kai Sievers, M.D Department of Hygiene and Social Medicine, University of Oulu has gone over certain passages of the book with me and suggested useful corrections. I thank him for his interest and help

The manuscript was translated into English by Hilkka Kontiopää, M.A. (Helsinki) and John Suter Hon.B.A.Econ. (Dub.) My warmest thanks are due to them, to the personnel of th Medical Library University of Oulu who have helped me obtain the necessary literature and to the secretaries who have retyped the manuscript.

The study would not have been possible had not numerous physicians and nurses, unknown to me, carefully completed the relevant forms and questionnaires. This involved a great many extra working hours for already overworked staff My special gratitude is due to the chief physicians of the 21 pediatric hospitals concerned, whose support was required to make the study possible.

Financial support was received from the Ane and Signe Gyllenberg Foundation, Foundation for Pediatric Research in Finland, Medical Suppliers Orion Ltd., and Medical Research Foundation of Oulu. I am greatly indebted to them all.

Oulu, January 1969

GEORG ROSBERG

II SOCIO-ECONOMIC AND SOCIO-PSYCHOLOGICAL FACTORS IN MENTAL DISORDERS AND FUNCTIONAL SYMPTOMS

In both groups there were more frequently additional social and psychological factors in the hospital admission than admissions for purely medical indications

In the diagnosis group of mental disorders there were more boys than girls more children of 7—15 years of age than younger and more eldest children than others There were also more children of unmarried than married fathers and more children of fathers possessing a university degree than with lower educational level

In this diagnosis group there were more children from upper than from lower income families more children from such families which had a TV set than from families with no TV The same difference as in the ownership of a TV set was true of the ownership of a summer cottage The children had more frequently a distance from home to hospital exceeding 100 km than maximum 100 km

In mental disorders group children had to wait for admission more often and for a longer time than in other diseases There were often factors which delayed the discharge of the child from hospital Parents had often delayed hospital admission for economic reasons The child was taken to hospital more often too late than in time and the home care of the child was frequently neglected The children had already been in hospital more frequently than admitted for the first time for this disease

In the diagnosis group of functional symptoms there were less children under one year than one year and older There were more children between 7—15 years of age than under 7 years. The only child was admitted less frequently for functional symptoms than other children The group contained more children from families with one inhabitant per room than children from families with more than one inhabitant per room Children with a TV set at home were admitted more frequently than those who had no TV set at home. The ownership of a summer cottage had the same influence.

The group contained a larger number of children living at a distance of more than 100 km from hospital than children with a maximum distance of 100 km between home and hospital more children from Helsinki than from other communities and more children from North Finland than from South Finland

In hospitals with one pediatrician there were less children with functional symptoms than in other hospital types.

The children had to wait less frequently for more than one month than for a maximum of one month and admissions in time were more frequent than retarded admissions. Admissions of children whose care was neglected at home were less frequent than admissions of other children

27 Halloran, B. Emerson. II. A study with reference to certain physical, mental and social factors possibly associated with enuresis. *Acta Psychiat Scand*, 31 405, 1956

28 Hallman, N. and Wasz Höckert O Comparison between indications of hospitalization of children living in urban and rural districts. Lecture at *the XIth Intern Congr of Pediatrics*. Tokyo 1965

29. Hallman, N. and Wasz Höckert, O Indications for hospitalization of children in Finland. *Med Probl Pädiat*, IX 11 1965

30. Hare, E. H. Mental illness and social class in Bristol. *Brit J Prev Soc Med*, 9 191, 1955

31 Harrison, S. L., McDermott J F Wilson, P T and Schrager, J. Social class and mental illness in children. *Arch Gen Psychiat*, 13 411 1965

32 Hellström, R. Journerksamheten krä er specialister Många patienter söker utan remiss. *Läkartidningen*, 63 1369 1966

33. Helve, A., Koli, T Wegelius, R. and Wasz-Höckert O. Lastentarhalaisten infektioaltiuteen vaikuttavista tekijöista. (Factors influencing the susceptibility to infections in day-care center children) *Suomen Lääkärilehti Aik-L*, 2 27 1966

34 Hemanta, P Personal communication 1967

35. Hindelweit, H. T Oppenheim, A. N and Vince, P *Television and the child*. The Nuffield Foundation Oxford University Press, London, New York, Toronto 1958

36 Hollingshead, A. & Redlich, F C. *Social class and mental illness community study*. John Wiley & Sons, Inc New York 1958

37 Hultin, H. Socialmiljöns inverkan på barnets somatiska utveckling. *Socialmedicinsk tidskrift*, 44 1.0, 1967

38 Hunt G. R. Age, sex and service patterns in child guidance clinic. *J Child Psychol*, 2 185, 1961

39 Ingre, G. Sjukdomarnas förekomst inom olika sociala grupper *Socialmedicinsk tidskrift* 1 10, 1959

40. Inglis, D. and Marks, E. J Use of state mental hospitals as resource for children. *Amer J Orthopsychiat*, 28 689 1958

41 Jaco, E G. *The social epidemiology of mental disorders*. Russel Sage Foundation, New York 1960

42. Kaila, M. Nuorisorikollisuus. WSOY Porvoo, Helsinki 19.0

43 Kanterro, R. L. and Soravettula, M. Terveydentilan ja terveydenhoidon sosiaalisia taustatekijöitä (On social background factors of health condition and public health care) *Sosiaalilääketiet Aik L*, 3 25, 1965

44. Karlsson, G. *Sociologiska metoder* 2nd Ed. Svenska Bokförlaget, Stockholm 1963

45. Klapper, J. T *The effects of mass communication*. The Free Press of Glencoe, Illinois, 2nd Printing 1961

46. Klemetti, A. Relationship of selected environmental factors to pregnancy outcome and congenital malformations. *Ann Paediat Fenn*, 26 Suppl. 1966

47 Koos, E. L. Illness in Regionville. In Dorrian Apple (Editor) *Sociological studies of health and sickness*, New York, 1960

48. Koos, E. L. *Health in Regionville* Columbia University Press New York 1954

49 Korsch, B. M. Psychologic principles. Pediatrician and sick child. *Advances Pediat* 10 9 1958

50. Kutner, B. and Gordan, C. Seeking care for cancer *J Hlth hum Behav* 2 171 1961 In Coe, R. M. and Wessen, A. F Sociopsychological factors influencing the use of community health resources. *Amer J Publ Hlth*, 55 1024, 1965

51 Kuusi, P *60-luvun sosiaalipolitiikka*. WSOY Porvoo, Helsinki 1963

52. Levine, G. N. Anxiety about illness Psychological and social bases. *J Hlth hum Behav* 3 30, 1962 In Coe, R. M and Wessen, A. F Socio-psychological factors influencing the use of community health resources. *Amer J Public Hlth*, 55 1024 1965

53. Loja der, W Mattila, A. and Palmén, S. Om korrelationen mellan boendeförhållandens och vissa sanitära frågor *Nord Hyg T* 40 25, 1959

54 Lowe, L. H. *Families of children with early childhood schizophrenia*. *Arch Gen Psychiat*, 14 26, 1966

55 Lowe, C.R. and McKeown, T Incidence of infectious disease in the first three years of life, related to social circumstances. *Brit J Prev Soc Med*, 8 24 1954

56. MacKeith, R. and Sandler, J *Psychosomatic aspects of pediatrics*. Pergamon Press, Oxford, London, New York, Paris 1961

57 Maney A. C., Pace, R. and Morrison, D. F A factor analytic study of the need for institutionalization Problems and populations for program development. *Amer J Ment Defic*, 69 372, 1964

58. Martin, W J Vital statistics of the county of

References

1 AITKEN-SWAN J and PATERSON, R.: The cancer patient Delay in seeking advice. *Brit Med J* 1: 623 1955

2. ALAMERI, R. Ja POYHONEN P *Jakdatusta t lastollisen tutkimuksen.* 4th ed. Print Oy Helsinki 1964

3. ALISON F FABIA, J and RAYNARD J *Enquête sur le enfant et les adolescents atteints d'infirmité motrice* Monographie de l Institut National d Hygiene. Paris 1961

4 ALLARDT E. and LITTUNEN Y *Sosiologia*, 3rd ed. WSOY Porvoo Helsinki 1964

5 AMNELL, G PALO, J and VARILO E. Vajaamielisyyden eli tymistiheys Suomessa (The epidemiology of mental deficiency in Finland) *Sosiaalilääketiet Aik L* 4 16, 1965

6 AMNELL, A L. *Elementar barnpsykiatri.* 2nd ed. Nordstedt & Soner Stockholm 1965

7 BARDY A nd KAUTTU, K. Tutkimus perinataaliseen kuolleisuuteen liittyvistä tekijöista. (Factors connected with per natal mortality) *Sosiaalilääketiet Aik L,* 3 125 1966

8. BLOK, S. and LEMPP R Die Stellung in der Geschwisterreihe und ihr Bedeutung fur das Auftreten psychoreaktiver Storungen. *Dtsch med J* 16 734 1965

9 BENDER I and GRUGETT A E. JR. A study of certain epidemiological factors in a group of children with early childhood schizophrenia. *Amer J Orthopsychiat* 26 131 1956

10. BERFENSTAM R. and WILL ER, I Ensam mor i 60-talets samhalle. *Socialmedicinsk tidskrift* 43 370 1966

11 BROWNING, R. H. and NORTHCOTT T J *On the season Jacksonville Florid tate board f health,* 1961
In COE, R M and WESSEN, A F Socio-psychological factors influencing the use of community health resources. *Amer J Publ Hlth,* 55 1024 1965

12 CHASKEL, R Changing patterns of services for unmarried parents. *Social casework* 49 5, 1968

13. CHRISTENSEN V: Child morbidity in a good and a bad residential area. *Dan med Bull,* 3 93 1956

14 COE, R. M and WESSEN, A F Socio-psychological factors influencing the use of community health resources. *Amer J Publ Hlth,* 55 1024 1965

15 DVORKOVSKY S Vad betyder numret syskonskaran. *Socialmedicinsk tidskrift* 43 11 1966

16. EATON L. Hospitalizing emotionally disturbed children. *Postgrad Med,* 41 599 1967

17 EISENBERG L. The str tegic deployment of the child psychiatrist in preventiv psychiatry *J Child Psychol Psychiat* 2 229 1961

18. EKSTROM, G and NYLANDER, I Appendectomy of children with nervous abdominal pain. *Acta Paedopsychiat* 28 210, 1961

19 FARBER, B. Effects of a severely mentally retarded child on family i tegration. In: Mercer J R.: Patterns of family crisis related t reacceptance of the retardate. *Amer J Ment Defic* 71 19 1966

20 FARIS, R. E. and D NHAM H. W *Mental disorders in urban areas* Chicago, 1939 (Cited by *Inghe 1959)*

21 FELDSTEIN, M. S. and BUTLER, N R. Analysis of factors affect ng perinatal mortality *Brit J Prev Soc Med* 19 1 8, 1965

22 FRISK, M. *Tonåringsproblem* Samfundet Folkhalsan, Boktrycker Ab Versal Helsinki 1968

23. GOLDSON, R. K. G RHAR P R. nd HANDY V H Some factors related to patient delay in seeking diagnosis for cancer symptoms. *Cancer (Philad.)* 10 1 1957

24 GRAD, J nd SAINSBURY P Problems of caring for the mentally ill t home *Proc Roy Soc Med,* 59 20 1966

25. GRAHAM, S. Socio-economic status, illness and the use of medical services. In Jaco E. G. *Patients physicians and illness,* Glencoe Illinois 1958

26. HAA TO-MANNILA, E. *Kotona seurattuun lapsiin Suomen maaseudulla.* Maalaisk tien Liiton Kirjapaino, Helsinki 1962

27 Hallgren, B. Enuresis. II. A study with reference to certain physical, mental and social factors possibly associated with enuresis. *Acta Psychiat Scand*, 31 405, 1956

28. Hallman, N and Ware-Hockert, O.: Comparison between indications of hospitalization of children living in urban and rural districts. Lecture at *the XIth Intern Congr of Pediatrics*, Tokyo 1965

29. Hallman, N and Ware-Hockert O Indications for hospitalization of children in Finland. *Mod Probl Pädiat* IX 11 1965

30. Hare, E. H. Mental illness and social class in Bristol. *Brit J Prev Soc Med*, 9 191 1955

31 Harrison, S. L., McDermott J F Wilson P T and Schrager, J Social class and mental illness in children. *Arch Gen Psychiat*, 13 411 1965

32. Hellström, R. Jourverksamheten kräver specialister Många patienter söker utan orsak. *Läkartidningen*, 63 1369, 1966

33. Hel... A., Koli, T Wrobel..., R. and Ware Hockert O Lastentarhalaisten infektioalttiuteen vaikuttavista tekijöistä. (Factors influencing the susceptibility to infections in daycare center children) *Sosiaalilääketiet Aik L*, 2 27 1966

34. Hemanus, P Personal communication 1967

35. Hinselwood H. T Oppenheim, A. N. and Vince, P *Television and the child*. The Nuffield Foundation Oxford University Press, London, New York, Toronto 1958

36. Hollingshead, A. & Redlich, F C. *Social class and mental illness community study*. John Wiley & Sons, Inc. New York 1958

37 H ... H. Socialmiljöns inverkan på barnens somatiska utveckling. *Socialmedicinsk tidskrift* 44 150, 1967

38. H ... G R. Age, sex and service patterns in child guidance clinics. *J Child Psychol*, 2 185, 1961

39 Inghe, G. Sjukdomarnas förekomst inom olika sociala grupper *Socialmedicinsk tidskrift* 1 10, 1959

40 Inglis, D. and Marsh, E. J Use of state mental hospitals as resource for children. *Amer J Orthopsychiat*, 28 688, 1958

41 Jaco, E G *The social epidemiology of mental disorders* Russel Sage Foundation, New York 1960

42 Kaila, M. Nuorisorikollisuus. WSOY Porvoo Helsinki 1950

43 Kantero, R. L. and Son ... ttula, M. Terveydentilan ja terveydenhoidon sosiaalisia taustatekijöitä (On social background factors of health condition and public health care) *Sosiaalilääketiet Aik L*, 3 25, 1965

44. Karlsson, G. *Sociologiska metoder* 2nd Ed. Svenska Bokförlaget, Stockholm 1965

45. Klapper, J. T *The effects of mass communication*. The Free Press of Glencoe, Illinois, 2nd Printing 1961

46. Klemetti, A. Relationship of selected environmental factors to pregnancy outcome and congenital malformations. *Ann Paediat Fenn*, 26 Suppl. 1966

47 Koos, E. L. Illness in Regionville. I : Dorrian Apple (Editor) *Sociological studies of health and sickness*, New York, 1960

48. Koos, E. L. *Health in Regionville* Columbia University Press New York 1954

49. Korsch, B. M. Psychologic principles. Pediatrician and sick child. *Advances Pediat* 10 9 1958

50. Kutner, B. and Gordan, G. Seeking care for cancer *J Hlth hum Behav* 2 171 1961
I Coe, R. M. and Wessen, A. F Sociopsychological factors influencing the use of community health resources. *Amer J Publ Hlth*, 55 1024, 1965

51 Kuusi, P *60-luvun sosiaalipolitiikka*. WSOY Porvoo, Helsinki 1963

52. Levine, G. N. Anxiety about illness Psychological and social bases. *J Hlth hum Behav* 3 30, 1962. I Coe, R. M. and Wessen, A. F : Socio-psychological factors influencing the use of community health resources. *Amer J Public Hlth*, 55 1024, 1965

53 Lojander, W Mattila, A. and Palmén, E. Om korrelationen mellan bostadsförhållandena och vissa sanitära frågor *Nord Hyg T* 40: 25, 1959

54. Lowe, L. H. Families of children with early childhood schizophrenia. *Arch Gen Psychiat*, 14 26, 1966

55 Lowe, C.R. and McKeown, T Incidence of infectious disease in the first three years of life, related to social circumstances. *Brit J Prev Soc Med*, 8 24, 1954

56. MacKeith, R. and Sandler, J *Psychosomatic aspects of paediatrics*. Pergamon Press, Oxford, London, New York, Paris 1961

57 Mabe A. C., Page, R. and Morrison, D F A factor analytic study of the need for institutionalization: Problems and populations for program development. *Amer J Ment Defic*, 69 372, 1964

58. Martin, W J Vital statistics of the county of

London in the years 1901 to 1951 *Brit J Prev Soc Med* 9: 126, 1955
59 MASTROPAOLO, C. The role of the father in juvenile delinquency *World Med J* 14 89 1967
60 MCDERMOTT J F Jr HARRISON S. I SCHRAGER, J LINDY J and KILLINS, E.: Social class and mental illness n children The question of childhood psychosis. *Amer J Orthopsychiat* 37: 548 1967
61 MCDERMOTT J F HARRISON S. I SCHRAGER J and WILSON P Social class and mental illness i children Observations of blue-collar families. *Amer J Orthopsychiat* 35: 500 1965
62. MCNEMAR, Q *Psychological statistics* Wiley 2nd Ed. New York 1955
63 MECHANIC, D The concept of illness behavior *J Chronic Dis* 15 189 1961
64 MERCER J F Patterns of family crisis elated to reaccept nce of the retardate. *Amer J Ment Defic* 71 19 1966
65 MERRILL, M H HOLLISTER A G. GIBBENS, S. L. and HAYNES, A. V Attitudes of Califor nians t ward poliomyel tis vaccination. *Amer J Public Health*, 18 146, 1958
66 MILLER D *Problems f adolescents.* Personal comm nication, 1967
67 MILLER, F J W COURT S. D M WALTON W S. and KNOX, E. G *Growing up in Newcastle—upon—Tyne. A continuing tudy of health and illness in young children within their familie* Th Nuffield Fou datio Oxford University Press, London, New York Toront 1960
68 MITTLER P nd WOODWARD M The education of h ldren n hospitals for the subnormal A survey of admissions. *Develop Med Child Neurol* 8 16, 1966
69 *Nomenclatura tatistica internationalis morborum et traumatum et causarum morbis* Valtioneuvoston kirjapa no, Helsinki 1953 (WHO 1948)
70 NYMAN, K *Lasten lääkäripalvelusten käytön sosiaaliset taustatekijät Suomessa ennen sairausvakuutusta.* Kansaneläkelaitoksen julkaisusarja M 10/1968 Helsinki 1968
71 OLKINUORA, M. Epidemiologisia näkökohtia psykiatriassa. *Duodecim (Helsinki)* 82 145 1966
72 OLTMAN, J E. nd FR DMA S. Trends admissions t tat hospital 1942—1964 *Arch Gen Psychiat*, 13 544 1965
73 PAAVOLA, A. The illegitimacy rat and factors influenc ng the pregnancy and delivery of unmarried others. *Acta Obstet Gynec Scand* 47 suppl 3 1968
74 PALMGREN, K. *Kehittyneisyyden alueellisista eroavaisuuksista Suomessa. (Regional differences in the degree of development in Finland)* Valtakunnan suunnittelutoimiston julkaisusarja A 15 Helsinki 1964
75 PELTONEN, T Über die sogenannten funktionellen Störungen im Schulalter *Ann Paediat Fenn*, 2 suppl. 7 1956
76. PUROLA, T KALIMO E. SIEVERS, K. nd NYMAN K. Sairastavuus ja lääkintäpalvelusten käyttö Suomessa ennen sairausvakuutusta. Kansaneläkelaitoksen julkaisusarj 1/1967 Helsinki 1967
77 RANTASALO V and VALPOLA, H. Sosiaalisista tekijöistä lasten sairaalahoidon iheuttajina. *Duodecim (Helsinki)* 873, 1955
78. ROSBERG G WAHLSTRÖM HÖCKERT O and HALLMAN N Mother's role in child' hospital admission with special referenc to psychic diseases and functional symptoms. *First Scandinavian Congress f Social Medicine* Gothenburg 1967
79 ROSBERG G Psykologiset tekijät lasten sairaalaan otossa. *Suom Lääk* 23: 99 1968
80 SAENGER, G Factors influencing the institutionalizing of mentally retarded individuals in New York City In: Mercer J R.: Patterns of family crisis related t reacceptance of the retardat *Amer J Men Defic* 71: 19 1966
81 SARASON S B and GLADWIN T : Psychological and cultural problems i mental subnormal ty *Amer J Ment Defic* 62 1115, 1958
82 *Seminar on hospitalization of children.* Mod. Probl. P ediat. Vol IX. Karger Basel, New York 1965
83. SHEPHERD M OPPENHEIM, A. N nd MITCHELL, S. Childhood behaviour disorders nd the ch ldguidance clinic An epidem ological study *J Child Psychol Psychiat*, 7 39 1966
84 SIIRALA, M Perusk atsom kemme merkityksestä lääketieteessä (O the importance of our basic views in medicine.) *Sosiaalilääketiet Aik L*, Suppl II 1966
85. SIMON, N and RABUSHKA, S. Membership ttitudes in the labor health ... in St Louis. *Amer J Public Health* 46 716, 1956
86. SIMMONS, L. W and WOLFF H G *Social science in medicine* Russel Sage Foundation New York 1954
87 SJÖLIN, S. The problem of overlong st y i hospital. *Mod Probl Paediat* IX 161 1965
88. SPENCE, J WALTON W S. MILLER F J W nd COURT S. D M. *A thousand families in Newcastle—upon—Tyne.* Oxford U ersity Press, London, N w York, Toront 1954
89. SROLE, L. LA ER, T S. M CHAEL, S. F

Opler, M. K., and Rennie, T. A. C. *Mental health in Metropolis.* McGraw Hill, New York 1962

90. Strömgren, A. and Achté, K. A. An epidemiological study of psychiatric morbidity in Helsinki. In Report on the fourteenth congress of Scandinavian psychiatrists. *Acta Psychiat Scand*, Suppl 180, 1963

91. Strömgren, A. and Achté, K. A. Hospital first admissions and social class. *Acta Psychiat Scand* 42 113, 1966

92. Straus, P Coiffard, N., Marzo-Weyl, S. and Lenoir, M. *L hospitalisation des enfants, Une étude de pédiatrie sociale dans l'agglomération parisienne.* Monographie de L'Institut National d'Hygiène No 23, Paris 1961

93. Suchman, E. A. Social patterns of health and medical care. New York City Department of Health 1963. In Coe, R. M. and Wessen, A. F Sociopsychological factors influencing the use of community health resources. *Amer J Public Health*, 55 1024 1965

94. *Suomen tilastollinen vuosikirja 1965. Statistical year book of Finland 1965.* Valtioneuvoston kirjapaino, Helsinki 1966

95. Söderling, B. Några sociala orsaker till psykosomatiska besvär ... allmän läkarpraxis. *Läkartidningen*, 49 102, 1952

96. Taipale, L. *Suomen vajaamieliset ja heidän hoidontarpeensa* (The mentally subnormal and their need for care in Finland.) Helsinki 1966

97 *The child in Finnish society* Central Union for Child Welfare in Finland Helsinki 1963

98. Tizard, J Mental subnormality and child psychiatry *J Child Psychol* 7 1 1966

99. U.S. Public Health Service. National health survey *acute conditions, incidence and associated disability* Ser 10. No 10 Washington, 1964 I Coe, R. M. and Wessen, A. F Sociopsychological factors influencing the use of community health resources. *Amer J Public Health*, 55 1024 1965

100. Valanne, E. Lastenpsykiatrisesta konsultatiosta lastensairaalassa. *Suom Lääk*, 17 1533, 1961

101 Vernon, D. T A., Foley J M., Sipowicz, R. R., Schulman, J L. *The psychological responses of children to hospitalization and illness.* Charles C. Thomas Publisher Springfield, Illinois 1965

102. Vorkamook, R. P and Wescis, R. Social class and length of hospital stay of first-admission psychiatric patients. *Ment Hyg* 51 580, 1967

103. Vähä ..., L. Sosiaaliset tekijät ja lasten sairaalahoito. *Suppl. Duodecim 1962.* (Social factors and hospital admission rate of children) *Ann Paediat Fenn*, Suppl. 1963

104 Waris Hooker O Juntunen, O and Saloaara, H. Social conditions and public health care in North and South Finland according to statistics. *Ann Hyg Med Soc Fenn*, 1 1 1963

105. *Yleinen terveyden- ja sairaanhoito (Public health and medical care) 1962—63.* The official statistics of Finland. Valtioneuvoston kirjapaino, Helsinki 1965

106. *Yleissairaaloiden käyttö Suomessa vuonna 1960 (Utilization of general hospital services in Finland 1960)* Lääkintöhallituksen tutkimuksia 1/1966, Helsinki 1966

London in the years 1901 to 1951 *Brit J Prev Soc Med* 9: 126, 1955
59 MASTROPAOLO, C. The role of the father in juvenile delinquency *World Med J* 14 89 1967
60 McDERMOTT J F Jr HARRISON, S. I SCHRAGER, J LINDY J and KILLINS, E.: Social class and mental illness in children The question of childhood psychosis. *Amer J Orthopsychiat* 37 548, 1967
61 McDERMOTT J F HARRISON, S. I SCHRAGER J and WILSON, P Social class and mental illness in children: Observations of blue-collar families. *Amer J Orthopsychiat* 35: 500, 1965
62 McNEMAR, Q *Psychological statistics.* Wiley 2nd Ed New York 1955
63 MECHANIC, D: The concept of illness behavior *J Chronic Dis* 15 189 1961
64 MERCER, J F: Patterns of family crisis related t reacceptance of the retardate. *Amer J Ment Defic* 71: 19 1966
65. MERRILL, M. H HOLLISTER, A. C. GIBBENS, S. L. nd HAYNES, L. V Attitudes of Californians toward poliomyelitis vaccination. *Amer J Public Health*, 48: 146, 1958
66 MILLER, D *Problems f adolescents.* Personal communication 1967
67 MILLER, F J W COURT S. D M WALTON W S. and KNOX, E. G *Growing up in New castle—upon—Tyne. A continuing study of health and illness in young children within their families* The Nuffield Foundation, Oxford Uni ersity Press, London, New York, Toronto 1960
68 MITTLER, P and WOODWARD, M The educa tion of h ldren in hospitals for the subnormal A urvey of admissions. *Develop Med Child Neurol* 8 16, 1966
69 *Nomenclatur tatistic internationalis morborum et traumatum et causarum morbis.* Valtioneuvoston kirjapaino Helsink 1953 (WHO 1948)
70 NYMAN K. *Lasten laakarinpalvelusten kaytto sosiaaliset tautiatelty t Suomessa ennen sairausvakuutusta.* Kansaneläkelaitoksen julkaisusarja M 10/1968 Helsi ki 1968
71 OLKINUORA, M Epidemiologisia nakokohtia psykiatriassa. *Duodecim (Helsinki)* 82 145 1966
72 OLTMAN J E. and FRIEDMAN S. Trends admissions to stat hospital 1942—1964 *Arch Gen Psychiat* 13 544 1965
73 PAAVOLA, A. The illegitimacy rat and factors influencing the pregnancy and delivery of unmarried mothers. *Acta Obstet Gynec Scand* 47 suppl. 3, 1968
74 PALMGREN K. *Kehityserojen alueittaiset erot maakunta Suomessa. (Regional differences in the degree of development in Finland)* Valtakunnan suunnittelutoimiston julkaisusarja A 15, Helsinki 1964
75 PELTONEN, T Über die sogenannten funktionellen Störungen im Schulalter *Ann Paediat Fenn*, 2 suppl. 7 1956
76 PUROLA, T KALIMO E. SIEVERS, K. and NYMAN K. Sairastavuus ja lääkintäpalvelusten käyttö Suomessa ennen sairausvakuutusta. Kansaneläkelaitoksen julkaisusarja 1/1967 Helsinki 1967
77 RANTASALO, V and VALPOLA, H.: Sosiaalisista tekijöistä lasten sairaalahoidon aiheuttajina. *Duodecim (Helsinki)* 873, 1955
78. ROSBERG G. WARE HÖCKERT O and HALLMAN, N Mother le in ch ld s hospital admission w th special reference to psychic diseases and functional sympt ms. *First Scandinavian Congress f Social Medicine* Gothenburg 1967
79 ROSBERG, G Psykologiset tekijät lasten sairaalaan toista. *Suom Lääk*, 23: 99 1968
80. SAENGER, G. Factors influencing the institutionalizi g of mentally retarded individuals in New York City In Mercer J R. Patterns of family crisis related t reacceptance of the retardate. *Amer J Men Defic* 71 19 1966
81 SARASON, S. B. and GLADWIN, T Psychological and cultural problems in mental subnormality *Amer J Ment Defic* 62 1115, 1958
82 *Seminar on hospitalization f children.* Mod. Probl. Paediat Vol IX. Karger Basel, New York 1965
83. SHEPHERD, M. OPPENHEIM, A. N nd MITCHELL, S. Childhood behaviour disorders and th childguidance clinic A epidemiological study *J Child Psychol Psychiat*, 7 39, 1966
84 SIIRALA, M Peruskatsom ksemme merkityksestä lääketieteessä (On the importance of our basic view in medicine.) *Sosiaalilääketiet Aik L*, Suppl. II 1966
85. SIMON, N and RABUSHKA, S M mbership att tudes in the labor health institut t St Louis. *Amer J Public Health*, 46 716, 1956
86. SIMMO s, L. W and WOL H G *Social science in medicine* Russel Sage Foundation New Y rk 1954
87 SJO M, S. Th problem of overlong stay hospital. *Mod Probl Paediat* IX 161 1965
88. SP NCE, J WALTON, W S. M LLER F J W and CO RT S. D M. *A thousand families in Newcastle—upon—Tyne* Oxford University Press, London, New York, Toronto 1954
89. SROLE, L. LANGNER, T S. MICHAEL, S T

INVESTIGATION OF INDICATIONS FOR HOSPITAL ADMISSION OF CIHLDREN

CODES

JOURNAL NO.

HOSPITAL AND WARD

DATE OF ADMISSION ____/____ 19__

SEX (CROSS)
- 1 GIRL
- 2 BOY

IS THE CHILD
- 1 LEGITIMATE
- ILLEGITIMATE

CHILD'S AGE ON ADMISSION

- UNDER 15 DAYS
- ONE MONTH
- 2 MONTHS
- 3 MONTHS
- 4–5 MONTHS
- 6–11 MONTHS
- 12–17 MONTHS
- 18–24 MONTHS
- 30 MONTHS
- 3 YEARS
- 42 MONTHS
- 4 YEARS
- 54 MONTHS
- 5 YEARS
- 6 YEARS
- 7 YEARS
- 8 YEARS
- 9 YEARS
- 10 YEARS
- 11 YEARS
- 12 YEARS
- 13 YEARS
- 14 YEARS
- 15 YEARS

CHILD'S DOMICILE

PARENTS'/FOSTER PARENTS' PRESENT OCCUPATION

FATHER

MOTHER

PARENTS'/FOSTER PARENTS' OCCUPATION BY INDUSTRY

FATHER	MOTHER	
1	1	AGRICULTURE AND FORESTRY FISHING
2	2	MANUFACTURING INDUSTRY (INCL. ELECTRICITY GAS AND WATER SERVICES, HANDICRAFT
3	3	BUILDING
4	4	COMMERCE
5	5	COMMUNICATIONS
6	6	SERVICES (SOCIAL, INDUSTRIAL, PRIVATE)
7	7	NO OCCUPATION
8	8	NOT KNOWN

14. PARENTS'/FOSTER PARENTS' OCCUPATIONAL POSITION

THER	MOTHER	
1	1	EMPLOYED, SELF-EMPLOYED
2	2	MANAGER, EXECUTIVE
3	3	WORKER
		ASSISTING FAMILY MEMBER
5	5	NO OCCUPATION
6	6	NOT KNOWN

CODES

INVESTIGATION OF INDICATIONS FOR HOSPITAL ADMISSION OF CIHLDREN

JOURNAL NO.

6 | 7

HOSPITAL AND WARD

DATE OF ADMISSION ____/____ 19__

10 | 11

SEX (CROSS)

- [ ] GIRL
- [2] BOY

IS THE CHILD

- [ ] LEGITIMATE
- [2] ILLEGITIMATE

12 | 13

CHILD'S AGE ON ADMISSION

UNDER 5 DAYS	30 MONTHS	8 YEARS
ONE MONTH	3 YEARS	9 YEARS
2 MONTHS	42 MONTHS	10 YEARS
3 MONTHS	4 YEARS	[11] 11 YEARS
4—5 MONTHS	54 MONTHS	[12] 12 YEARS
6—11 MONTHS	5 YEARS	[13] 13 YEARS
12—17 MONTHS	YEARS	[14] 14 YEARS
18—24 MONTHS	7 YEARS	[15] 15 YEARS

14 | 15

CHILD'S DOMICILE

16 | 17

PARENTS'/FOSTER PARENTS' PRESENT OCCUPATION

18

FATHER ________

MOTHER ________

19

PARENTS'/FOSTER PARENTS' OCCUPATION BY INDUSTRY

ATHER	MOTHER	
	[1]	AGRICULTURE AND FORESTRY FISHING
[2]	[2]	MANUFACTURING INDUSTRY (INCL. ELECTRICITY, GAS AND W TER SERVICES), HANDICRAFT
[3]	[3]	BUILDING
[4]	[4]	COMMERCE
[5]	[5]	COMMUNICATIONS
[6]	[6]	SERVICES (SOCIAL, INDUSTRIAL, PRIVATE)
[7]	[7]	NO OCCUPATION
[8]	[8]	NOT KNOWN

PARENTS'/FOSTER PARENTS' OCCUPATIONAL POSITION

ATHER	MOTHER	
[1]	[1]	EMPLOYED, SELF-EMPLOYED
[2]	[2]	MANAGER, EXECUTIVE
[3]	[3]	WORKER
[4]	[4]	ASSISTING FAMILY MEMBER
[5]	[5]	NO OCCUPATION
[6]	[6]	NOT KNOWN

20 | 21

22 | 23

11 MARITAL STATUS OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE)

FATHER	MOTHER	
1	1	MARRIED
2	2	SINGLE
3	3	WIDOWER/WIDOW
4		JUDICIAL SEPARATION
5	5	DIVORCED
6	6	DEAD
7	7	NOT KNOWN

12. DO THE CHILD'S PARENTS LIVE IN THE CHILD'S HOME?

1	BOTH DO
2	MOTHER ONLY
3	FATHER ONLY
	CHILD LIVES WITH RELATIVES OR FOSTER PARENTS
	CHILD LIVES IN INSTITUTIONAL CARE (E.G. CHILDRENS' HOME)

24 25 26

13. AGE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE)

FATHER _ YEARS MOTHER YEARS

27 28 29 30

14. SCHOOL ATTENDANCE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE)

31 32

FATHER	MOTHER	
1	1	AMBULATORY SCHOOL ONLY
2	2	PRIMARY SCHOOL, LOWER FORMS
3		COMPLETE
		SECONDARY SCHOOL, LOWER FORMS
5	5	FIVE FORMS (MIDDLE SCHOOL)
		MORE THAN FIVE FORMS BUT NO MATRICULATION
	7	MATRICULATION, BUT NO UNIV. OR OTHER DEGREE
		UNIVERSITY OR OTHER DEGREE
9	9	NOT KNOWN

OTHER SCHOOLS

FATHER 33

MOTHER 34

15 DISTANCE FROM HOSPITAL TO CHILD'S HOME/NURSING HOME

1	UNDER 1/2 KM		16—30 KM
2	1/2—1 KM	7	31—100 KM
3	2—3 KM		101—200 KM
	4—10 KM		201 KM OR MORE
	11—15 KM		NOT KNOWN

16. DISTANCE FROM CHILD'S HOME/NURSING HOME TO THE NEAREST

35

a. NEIGHBOUR KM 36

b. TELEPHONE (UNLESS AT HOME) KM 37

MAJOR VILLAGE OR POPULATION CENTRE _ KM 38

d PHYSICIAN KM 39

17 MEANS OF TRANSPORT ONE OR SEVERAL, BY WHICH THE CHILD WAS BROUGHT TO HOSPITAL (CARRIED, BY PARENTS' CAR, TAXI, HORSE CART OR SLEIGH, CHAIR SLED ETC.) OVER WHAT DISTANCE KM

40 41 42 43

N.B. THE QUESTIONS ON THIS PAGE DO NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE (ITEM 12)

18. NUMBER OF YEARS THE FAMILY HAS LIVED IN ITS PRESENT DOMICILE

_____________ YEARS

44 45

19. SENIORITY OF THE CHILD AMONG SIBLINGS IF ANY _____________

[0] NO SIBLINGS

46 47

20. NUMBER OF CHILDREN UNDER 13 YEARS LIVING WITH THE CHILD'S FAMILY

_____________ CHILDREN

48 49 50 51

21. NUMBER OF FAMILY MEMBERS (ALL CHILDREN INCLUDED)

_____________ PERSONS

22. FACILITIES IN THE CHILD'S HOME

	YES	NO
a. ELECTRICITY	1	2
b. TELEPHONE	1	2
RUNNING WATER	1	2
d. TELEVISION	1	2
DOES THE FAMILY OWN		
e. PRIVATE CAR		2
f. SUMMER COTTAGE		2

52 53 54 55 56 57

23. NUMBER OF ROOMS AT THE FAMILY'S DISPOSAL, INCLUDING KITCHEN (BUT EXCLUDING KITCHENETTE, RECESS FOR BED, BATHROOM, LAVATORY AND ROOMS RENTED OUT)

_____________ ROOMS

58 59

24. PARENTS' MONTHLY EARNINGS, TOTAL

____
OLD/NEW MK

25. FOR CHILD LIVING IN FARMER FAMILY NUMBER OF HECTARES OF
a. THE FARM'S TOTAL AREA

_____________ HA

b. AREA UNDER PLOUGH

_____________ HA

60 61 62 63 64 65 66 67 68 69 70 71

26. IS MOTHER GAINFULLY EMPLOYED OUTSIDE HOME

[1] NO

[2] PRIMARILY PART-TIME

[3] FULL-TIME

COLUMN 6

72 73 74 75 76 77 78 79 80

27. IF MOTHER IS EMPLOYED OUTSIDE HOME, IS THE CHILD DURING MOTHER'S WORKING HOURS

[1] AT HOME TENDED BY SOMEONE ELSE

[2] AT HOME ALONE OR WITH OTHER CHILDREN

[3] IN DAY NURSERY OR THE LIKE

[4] IN RELATED OR OTHER FAMILY

CARD 3

1

11 MARITAL STATUS OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE)

FATHER	MOTHER	
1	1	MARRIED
2	2	SINGLE
3	3	WIDOWER/WIDOW
	4	JUDICIAL SEPARATION
5	5	DIVORCED
6	6	DEAD
7	7	NOT KNOWN

12. DO THE CHILD'S PARENTS LIVE IN THE CHILD'S HOME?

1	BOTH DO
2	MOTHER ONLY
3	FATHER ONLY
	CHILD LIVES WITH RELATIVES OR FOSTER PARENTS
5	CHILD LIVES IN INSTITUTIONAL CARE (E.G. CHILDRENS' HOME)

2 | 25 | 26

13. AGE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE)

FATHER YEARS MOTHER YEARS

27 | 28 | 29 | 30

14. SCHOOL ATTENDANCE OF PARENTS/FOSTER PARENTS (DOES NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE)

FATHER	MOTHER	
1		AMBULATORY SCHOOL ONLY
2	2	PRIMARY SCHOOL, LOWER FORMS
3	3	COMPLETE
		SECONDARY SCHOOL, LOWER FORMS
5		FIVE FORMS (MIDDLE SCHOOL)
		MORE THAN FIVE FORMS BUT NO MATRICULATION
		MATRICULATION, BUT NO UNIV OR OTHER DEGREE
	8	UNIVERSITY OR OTHER DEGREE
9	9	NOT KNOWN

31 | 32

OTHER SCHOOLS

FATHER

MOTHER

33 | 34

15 DISTANCE FROM HOSPITAL TO CHILD'S HOME/NURSING HOME

	UNDER 1/2 KM		16—30 KM
2	1/2—1 KM	7	31—100 KM
3	2—3 KM		101—200 KM
	4—10 KM	9	201 KM OR MORE
5	11—15 KM	0	NOT KNOWN

35

16. DISTANCE FROM CHILD'S HOME/NURSING HOME TO THE NEAREST

NEIGHBOUR KM

b TELEPHONE (UNLESS AT HOME) KM

MAJOR VILLAGE OR POPULATION CENTRE — KM

d. PHYSICIAN KM

36 | 37 | 38 | 39

17 MEANS OF TRANSPORT ONE OR SEVERAL BY WHICH THE CHILD WAS BROUGHT TO HOSPITAL (CARRIED BY PARENTS' CAR, TAXI, HORSE CART OR SLEIGH CHAIR SLED ETC.) OVER WHAT DISTANCE KM

40 | 41 | 42 | 43

N.B. THE QUESTIONS ON THIS PAGE DO NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE (ITEM 12)

36. WERE THE PARENTS OPPOSED TO THE CHILD'S HOSPITALIZATION? | 32 | 33

MOTHER	FATHER	
1	1	NO
2–9	2–9	YES, FOR THIS REASON ______________________
0		CANNOT SAY

37. HAVE THE CHILD'S PARENTS BEEN TREATED IN HOSPITAL FOR ILLNESS (EXCLUDING CHILDBIRTH) | 35

MOTHER	FATHER	
1	1	YES
2	2	NO
0		NOT KNOWN

38. HAS ANY OF THE CHILD'S SIBLINGS BEEN TREATED IN HOSPITAL FOR ILLNESS | 36

1	YES
2	NO ONE
	THERE ARE NO SIBLINGS
	NOT KNOWN

39. WHO WAS/WERE INTERVIEWED

40. ADDITIONAL INFORMATION

DATE ______ ______ 196__

____
INTERVIEWER'S NAME AND POSITION

N.B. THE QUESTIONS ON THIS PAGE DO NOT APPLY TO CHILDREN IN INSTITUTIONAL CARE (ITEM 12)

28. IF MOTHER IS EMPLOYED OUTSIDE HOME, HOW LONG HAS SHE BEEN SO EMPLOYED — 7

__ __ __ DAYS/WEEKS/MONTHS/YEARS

29. HOW LONG DID THE CHILD SUFFER FROM THIS ILLNESS AT HOME, BEFORE ADMISSION TO HOSPITAL — 8

__ __ __ DAYS/WEEKS/MONTHS/YEARS

30. HAS THE CHILD BEEN PREVIOUSLY TREATED IN HOSPITAL FOR THIS ILLNESS — 9

- [ ] YES
- [1] NO

31. WHO WAS FIRST CONSULTED FOR MEDICAL HELP AFTER THE CHILD HAD FALLEN ILL — 10

- [1] PHYSICIAN
- [2] PUBLIC HEALTH NURSE/MIDWIFE/DEACONESS
- [3] HEALER
- [ ] PHARMACY
- [5–9] SOMEONE ELSE

HOW LONG HAD THE ILLNESS LASTED BY THEN — 11

DAYS/WEEKS/MONTHS/YEARS

32. HAD SOMEONE ADVISED THE PARENTS TO TAKE THE CHILD TO HOSPITAL — 12

- [1] NO ONE
- [2] PHYSICIAN
- [3] NURSE, PUBLIC HEALTH NURSE, DEACONESS, HOUSEKEEPER ETC.
- [ ] HEALER
- [5] MOTHER-IN-LAW THE CHILD'S MATERNAL OR PATERNAL GRANDMOTHER
- [6] SOMEONE ELSE
- [0] NOT KNOWN

33. WAS PHYSICIAN CONSULTED FOR THE CHILD'S ILLNESS — 13

- [ ] YES
- [2] NO

34a. DID PARENTS POSTPONE TAKING THE CHILD TO HOSPITAL FOR FEAR OF EXPENSES — 14

- [ ] YES
- [ ] NO
- [ ] CANNOT SAY

b. FOR SOME OTHER REASON — 15

35. ARE THE CHILD'S PARENTS AND SIBLINGS AT THE MOMENT HEALTHY SICKLY OR ILL¹) — 16, 17, 18, 19, 20, 21

	FATHER	MOTHER	SIBLINGS: ELDEST	2	3		5			8
HEALTHY		4								
SICKLY	2									
ILL	3	6								

	SIBLINGS	10		12	13
HEALTHY					
SICKLY					
ILL					

¹) Healthy here refers to a person who does not consider himself ill and manages his everyday work satisfactorily. Sickly here refers to a person whose disturbed state of health does not appreciably affect his ability of managing his everyday work satisfactorily. Ill refers to a person who due to his disturbed state of health is unable to manage his everyday work.

TO BE COMPLETED BY PHYSICIAN ON THE CHILD'S DISCHARGE
(or at the latest, on the day the form is due to be returned)

1. DIAGNOSIS A OUTPATIENT CLINIC ON ADMISSION | 33 | 36

DIAGNOSIS ON DISCHARGE (IF DISCHARGED) | 37 | 38

DO YOU FIND THAT THE CHILD WAS ADMITTED (CROSS) | 39

[ ] ON PURELY MEDICAL INDICATIONS

[2] PARTLY ALSO FOR SOCIAL REASONS

[3] DECISIVELY FOR SOCIAL REASONS

[4] PARTLY OR DECISIVELY DUE TO PSYCHOLOGICAL FACTORS IN THE FAMILY

DO YOU FIND THAT THE PARENTS | 40

[1] CONSULTED THE PHYSICIAN / THE HOSPITAL IN TIME

[2] CONSULTED THE PHYSICIAN / THE HOSPITAL TOO LATE

DO YOU FIND THA THE CHILD HAD APPARENTLY BEEN NEGLECTED AT HOME | 41

[1] YES

[2] NO

COULD THE CHILD HAVE BEEN DISCHARGED EARLIER?
(TO BE COMPLETED ONLY IF THE CHILD HAS BEEN DISCHARGED) | 42

[1] YES, IF THE CHILD'S HOME CONDITIONS HAD BEEN BETTER

[2] YES, IF THE CHILD'S HOME HAD BEEN BETTER LOCATED

[4] YES, HAD THE CHILD NOT ACQUIRED AN INFECTION IN HOSPITAL

[3] YES, IF THERE HAD BEEN NO WAITING PERIOD BEFORE EXAMINATIONS

[6-8] YES, IF THE FOLLOWING CONDITIONS HAD BEEN MET ______________

____

[2] NO

DATE ____/____ 19__

____
PHYSICIAN'S SIGNATURE

TO BE COMPLETED BY WARD SISTER ON THE CHILD'S DISCHARGE

(or at th latest, on the day the form is due to be returned)

	27	28	29
40. IF THE CHILD HAS BEEN DISCHARGED HOW LONG DID HE STAY __ __ __ __ DAYS IF HE HAS NOT BEEN DISCHARGED, HE REMAINED IN THE HOSPITAL ON (DATE) __ __ / __ __ 196__			

	30
41. HOW LONG DID THE CHILD HAVE TO WAIT FOR ADMISSION __ __ __ DAYS/WEEKS/MONTHS	

	31
42. WAS THE PARENTS'/FOSTER PARENTS' ATTITUDE TO HOSPITAL AND HOSPITAL PERSONNEL [1] FAVOURABLE [2] INDIFFERENT [3] NEGATIVE [0] IMPOSSIBLE TO SAY [9] THE CHILD CAME FROM AN INSTITUTION	

43. WAS THE PARENTS'/FOSTER PARENTS' ATTITUDE TO THE CHILD

FATHER	MOTHER		32	33
1	1	UNUSUALLY PROTECTIVE		
2	2	UNUSUALLY SPOILING		
3	3	NORMAL		
		SLIGHTING OR INDIFFERENT		
0	0	IMPOSSIBLE TO SAY		
99		THE CHILD CAME FROM AN INSTITUTION		

	34
44. ON DISCHARGE THE CHILD WAS [1] CONVALESCENT [2] UNIMPROVED [3] UNTREATED [ ] DEAD [8] REMAINED IN HOSPITAL AFTER THE FORM WAS RETURNED	

DATE __ / 196

__ WARD SISTER'S SIGNATURE

TO BE COMPLETED BY PHYSICIAN ON THE CHILD'S DISCHARGE

(or at the latest, on the day the form is due to be returned)

DIAGNOSIS T OUTPATIENT CLINIC ON ADMISSION — 25 | 26

DIAGNOSIS ON DISCHARGE (IF DISCHARGED) — 27 | 28

DO YOU FIND THAT THE CHILD WAS ADMITTED (CROSS) — 39

- [ ] ON PURELY MEDICAL INDICATIONS
- [2] PARTLY ALSO FOR SOCIAL REASONS
- [3] DECISIVELY FOR SOCIAL REASONS
- [4] PARTLY OR DECISIVELY DUE TO PSYCHOLOGICAL FACTORS IN THE FAMILY

DO YOU FIND THAT THE PARENTS — 40

- [1] CONSULTED THE PHYSICIAN / THE HOSPITAL IN TIME
- [2] CONSULTED THE PHYSICIAN / THE HOSPITAL TOO LATE

DO YOU FIND THAT THE CHILD HAD APPARENTLY BEEN NEGLECTED HOME — 41

- [1] YES
- [2] NO

COULD THE CHILD HAVE BEEN DISCHARGED EARLIER
(TO BE COMPLETED ONLY IF THE CHILD HAS BEEN DISCHARGED) — 42

- [ ] YES, IF THE CHILD'S HOME CONDITIONS HAD BEEN BETTER
- [ ] YES, IF THE CHILD'S HOME HAD BEEN BETTER LOCATED
- [ ] YES, HAD THE CHILD NOT ACQUIRED AN INFECTION IN HOSPITAL
- [ ] YES, IF THERE HAD BEEN NO WAITING PERIOD BEFORE EXAMINATIONS
- [ ] YES, THE FOLLOWING CONDITIONS HAD BEEN MET ____________
- [ ] NO

DATE ____/____ 19__

____
PHYSICIAN'S SIGNATURE

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 195 196

CEREBRAL SYMPTOMS IN THE NEWBORN

BY INGRID THORN

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

131. Mellbin, Tore The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw kr 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw kr. 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr 25.— 1962
134. Müller Tage, Short Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw kr 25.— 1962
135. *I Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet*, June 30, 1962. Sw kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw kr 25.— 1962
137 Hansen, A. E. Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review Sw. kr 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress*, Copenhagen. 1961. Edited by E. Winge Flensborg. Sw. kr 30.— 1963
141 Wass-Häckert, Ole and Dammer Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study Sw kr 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy A Clinical and Experimental Study Sw. kr 25.— 1963
144. Sterky Göran, Diabetic Schoolchildren. Sw. kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1962.* Sw. kr 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P Nylander I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply Sw. kr 20.— 1963
149. Valaes, Tinos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw kr. 25.— 1963
130. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization at the X International Congress of Paediatrics*, Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr 15.— 1963
152. Hjern, Bo and Nylander Ingvar Acute Head Injuries in Children Traumatology Therapy and Prognosis. Sw kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study Sw kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw kr 25.— 1964
157 Brante, G., Kaijser K. and Ockerman, P A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm. 1964. Edited by Y Larsson. Sw kr. 25.— 1965
160. Ockerman, P A., Glycogen Storage Disease in Sweden. Sw. kr 25.— 1965
161 Peltonen, T. and Hirvonen, L., Experimental Studies on F
and Neonatal Circulation. Sw. kr. 20.— 1965
162. Landmark, Karl Martin, Bone Marrow Cell Proliferation
Health and in Haematological Disease during Childhood.
kr. 25.— 1966
163. *Newborn Infant Cry* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactiv
and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J.
Bronchiectasis A Review of 187 Cases in Children with Follo
up Pulmonary Function Studies in 58. Sw kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheu
toid Arthritis. Analysis of 544 Cases. Sw. kr 15.— 1966
167 Iversen, Torben, Leukaemia in Infancy and Childhood. A M
rial of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W Focal Spike Discharges in Children, a Longitu
nal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right H
in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death
morphological and bacteriological study based on 264 autops
Sw kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chevrauh.* Sw kr. 35.— 1
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during
First Week of Life. Sw kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type
clinical study before and after operation with special refere
to haemodynamic function. Sw. kr. 25.— 1967
175. [illegible], Pentti, Vectorcardiographic Studies in Newborn
fants. Sw kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infecti
Sw. kr. 20.— 1967
177 *Proceedings of the Fifteenth Northern Pediatric Congress*, Berg
1967 Sw. kr. 15.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatric Practice w
Special Regard to Measurement of the Ventricular Size.
kr 28.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edi
by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody
sponse to *E. Coli* O-Antigens in Infants and Children w
Urinary Tract Infection, Using a Passive Haemagglutinat
Technique. Sw kr 20.— 1968
181. Koch, Günter Lung Function and Acid-Base Balance in
Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodologi
and Clinical Study. Sw kr. 25.— 1968
183. Robertson, Alex F., and Sprecher, Howard, A Review of Hu
Placental Lipid Metabolism and Transport. Sw kr. 25.— 1
184. Robertson, Bengt, The intrapulmonary arterial pattern in nor
infancy and in transposition of the great arteries. Sw kr. 2
1968
185. Andersen, Else, Skeletal Maturation of Danish School Child
in Relation to Height, Sexual Development, and Social Co
tions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Re
of the Literature and Report of Nine Cases. Sw. kr. 25.— 1
187 Karlberg, Petter, *et al.*, The Development of Children in
dish Urban Community. A Prospective Longitudinal Study I–
Sw kr. 30.— 1969
188. Meeuwisse, Gunnar W and Melin, Kerstin, Studies in Gluc
Galactose Malabsorption. A Clinical Study of 6 Cases and a
netic Study Sw. kr. 25.— 1969
189 Fällström, S. P., On the Endogenous Formation of Car
Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969
190. Hörnblad, P Yngve, Experimental Studies on Closure of
Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 2
1969
191. Koivikko, Antti, Cardiovascular Response of the Neonatal La
to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 3
1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Dise
in Children. Sw. kr 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and P
natal Mortality 1969
194. Kumento, Antti, Studies on the Serum Binding of Vitamin
in the Newborn Human Infant. Sw kr 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw kr. 1
1969
196. Rosberg, Georg, Social and Psychological Factors Influenc
Hospital Admission of Children. Sw. kr. 20.— 1969

Price Swed kr 20.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

Cerebral Symptoms in The Newborn

Cerebral Symptoms in The Newborn

Diagnostic and
prognostic significance of symptoms
of presumed cerebral origin

By
Ingrid Thorn

Munksgaard

Copenhagen 1969

To Peter and Soren

Denne afhandling er af det lægevidenskabelige fakultet ved Københavns universitet antaget til offentligt at forsvares for den medicinske doktorgrad

København den 19 november 1968

M Faber
h. a. dec.

PRINTED IN DENMARK BY
[illegible]

Preface

The present work was started at the Department of Paediatrics, The Copenhagen County Hospital in Gentofte. I thank the chief of the department, Dr med. *P W Brestrup* for inspiration and for much practical help.

The work continued during my appointment at the Department of Paediatrics of the University Hospital (Rigshospital) I thank Professor *P Plum* for experienced advice and for good working conditions.

Through the last stages of the work, while appointed to the Children s Hospital, Fuglebakken, I received much encouragement from the chief, Dr med. *H Andersen* for which I am grateful.

I also wish to express my thanks to the heads of the obstetrical departments of the University Hospital, Professor *E. Brandstrup* and Professor *D Trolle* for permission to use the records and for their interest.

I further thank Dr. *Inge Tygstrup* the Department of Pathology of the University Hospital, who willingly placed her meticulous pathological reports at my disposal.

For constant readiness in finding literature I wish to thank the staff at the University Library

Not least my thanks are due to the children and their parents for kind participation in the examinations.

The translation has been made by mrs. *B Damsgaard-Sørensen* medical secretary at the neurological department of the University Hospital, in cooperation with miss *Kathleen Larkin*, medical secretary London, and the author. I thank both for quick and good work.

Support by the Public Health Service Grant N B-02408 from The National Institute of Neurological Diseases and Blindness, Bethesda, U S. A. made possible a two months leave of absence.

Copenhagen, March 1969

Ingrid Thorn

Preface

The present work was started at the Department of Paediatrics, The Copenhagen County Hospital in Gentofte. I thank the chief of the department, Dr med. *P W Braestrup* for inspiration and for much practical help.

The work continued during my appointment at the Department of Paediatrics of the University Hospital (Rigshospital) I thank Professor *P Plum* for experienced advice and for good working conditions.

Through the last stages of the work, while appointed to the Children's Hospital, Fuglebakken, I received much encouragement from the chief, Dr med. *H Andersen* for which I am grateful.

I also wish to express my thanks to the heads of the obstetrical departments of the University Hospital, Professor *E Brandstrup* and Professor *D Trolle* for permission to use the records and for their interest.

I further thank Dr *Inge Tygstrup* the Department of Pathology of the University Hospital, who willingly placed her meticulous pathological reports at my disposal.

For constant readiness in finding literature I wish to thank the staff at the University Library

Not least my thanks are due to the children and their parents for kind participation in the examinations.

The translation has been made by mrs. *B Damsgaard-Sørensen* medical secretary at the neurological department of the University Hospital, in cooperation with miss *Kathleen Larkin* medical secretary London, and the author. I thank both for quick and good work.

Support by the Public Health Service Grant N B-02408 from The National Institute of Neurological Diseases and Blindness, Bethesda, U S. A. made possible a two months leave of absence.

Copenhagen, March 1969

Ingrid Thorn

Contents

Contents

Chapter V

Chapter VI

Chapter VII

Chapter VIII

Introduction

The diagnosis of neonatal disorders is fraught with great difficulty due to the non-specific reactions of the newborn to illness: one symptom may be caused by a variety of disorders, conversely one condition may present itself in a variety of ways, giving rise to multiple and severe symptoms, or only one symptom. Or it may be that a symptomless course will be followed by sudden death. Many unexpected diagnoses have been made on the autopsy table.

Because of the diagnostic difficulties, the incidence of perinatal cerebral damage is hard to establish and that of its sequelae even more so.

The challenge presented by these circumstances, as well as the severity of a number of the sequelae, are the motivation for the present study the purpose being an attempt to evalute the specificity and prognostic significance of supposedly cerebral symptoms in the newborn.

CHAPTER I

Previous studies of cerebral symptoms in the newborn

The most reliable information concerning the symptomatology of intracranial disorders in the newborn is offered by authors correlating clinical observations with autopsy findings.

Previous studies of this kind have been based on limited series. *McNutt (1885) examined 10* infants with intracranial haemorrhage. Nine had died within the first week of life, and the tenth when 22 days old. The clinical symptoms were not described in every case. It was emphasised that convulsions with haemorrhages over the convexity of the brain, were localized *and accompanied* by corresponding pareses, whereas they were generalized when the intracranial haemorrhages were found mainly at the base of the *brain* and around the cerebellum Convulsions, however were not necessarily present, and were especially rare with supratentorial haemorrhages. Among other inconsistent features were a refusal to nurse, cyanosis and irregular respiration

Seitz (1907) dealt with symptoms of increased intracranial pressure in 14 infants dying during the neonatal period On clinical grounds he, too, distinguished between supra and infratentorial haemorrhages. Patients with supratentorial haemorrhages, according to Seitz, were characterized by restlessness, crying and by a rigidity that was succeeded by flaccidity Moreover the fontanelle was tense. Infants with infratentorial haemorrhages, on the other hand, were apathetic, suffered from respiratory disorders and cyanosis as well as progressive spinal symptoms opisthotonus, rigidity and clonic convulsions. Seitz pointed out that the most severe cases of intracranial haemorrhage led to rapid death without preceding evidence of increased intracranial pressure. He also stated that cerebral oedema in the absence of haemorrhage might give rise to symptoms similar to those with cerebral haemorrhage.

Green (1914) presented a small series of patients with intracranial haemorrhage. He, too stressed the absence of symptoms in several cases. In other patients he had found refusal to nurse, pallor and facial oedema as initial symptoms, which might be followed by more "classical" symptoms.

Esch (1916) found, like Seitz, that cerebral haemorrhage and oedema might present identical symptoms and that many cases—whether fatal or not—were symptomless. He was not able to distinguish clinically between supratentorial and infratentorial haemorrhage. He did, however distinguish between early (i. e. present at birth) and late (i. e. developing within the first 24 hours) symptoms. As an early symptom frequently leading to early death he stressed severe respiratory disorders. Many late symptoms were severe and their outcome often fatal.

Brady (1918) and *Munro* and *Eustis* (1922) had made observations similar to those of Seitz. *Sidbury* (1920) found a similar symptomatology failed, however to distinguish between supratentorial and infratentorial haemorrhage. Both Brady and Sidbury concluded that the diagnosis was extremely difficult, and that intracranial haemorrhage should be borne in mind whenever the clinical picture was unclear

A major study of autopsy material was presented by *Heidler* (1927) consisting of 131 neonates dying from cerebellar tentorial tear In most cases he reported only apathy and feeble cry or even a complete absence of symptoms, particularly in premature infants. Irregular respiration, cyanosis and finally convulsions were noted. He was unable to distinguish between supratentorial and infratentorial haemorrhage. In 20 patients with leptomeningeal haemorrhage, five intraventricular and five intracerebral, he found a symptomatology similar to that seen in tentorial tear In six patients with brain contusion, oedema and hyperaemia the clinical features were pallor restlessness, irregular respiration and convulsions.

Dollinger (1927) discussed the difficulty of differential diagnosis due to "the monotony of the clinical pictures in different conditions, some of them extracerebral, and the diversity of clinical manifestations of the individual diseases. He experienced no diagnostic difficulty when an intracranial haemorrhage gave rise to what has later been referred to as Dollinger's "large picture with severe irritative or paretic symptoms. He stressed, however that in a great many cases of intracranial haemorrhage only the small picture was present, including debility and nutritional and pulmonary disorders. With small haemorrhages in the medulla he found respiratory difficulties. Cyanosis was found to be associated with respiratory disorders or small haemorrhages in the vasomotor centre. Convulsions were frequent, though they might be absent even with extensive haemorrhages. This was true also with disturbances of consciousness. He considered rigidity to be a spinal symptom.

Clein (1929) was concerned with the problems of differential diagnosis in premature infants. In 36 infants, who died in the neonatal period, he found intracranial haemorrhage in 21 and none in the remainder In the two groups there were differences in symptomatology in that cyanotic attacks were seen

only in infratentorial haemorrhage, and apathy was more pronounced in intracranial haemorrhage. Tremor was as frequent in intracranial haemor rhage as in extracerebral conditions (atelectasis or infections) Convulsions were seen in only three of the newborn who died, none showing cerebral damage.

Catel (1932) and *Liebe* (1940) established the diagnosis of intracranial haemorrhage on the basis of differences in the bilirubin concentration in blood and spinal fluid and found the validity of this method confirmed by autopsy findings in 34 and 68 infants respectively dying in the neonatal period. Both authors observed that some of the infants with intracranial haemorrhage failed to present any symptoms, and in patients with no intracranial haemorrhage similar symptoms might be observed as in those who had. They found, however that infants with intracranial haemorrhage frequently developed more symptoms but not enough to enable a diagnostic conclusion to be reached. Liebe regarded cyanosis, convulsions, refusal to nurse and decreased activity as non-specific symptoms, while delayed initial crying and intermittent loss of consciousness were more likely to be cerebral symptoms.

Rydberg (1932) observed that severe cerebral symptoms usually occurred after a symptomfree interval of hours or days poor nursing and apathy or intermittent or constant cyanosis as initial symptoms were followed by tremor rigidity convulsions, irregular respiration and high-pitched cry All symptoms, however were inconsistent. With a full clinical picture they were considered almost pathognomonic of intracranial haemorrhage. Such a pic ture was observed in 34 infants who died in the neonatal period. Six of these had no intracranial haemorrhage, but prominent degenerative tissue alterations were present in the brain. Rydberg further described an uncharacteristic picture which also developed after a symptomfree interval and was seen in a variety of diseases. It consisted of irregular respiration and cyanosis. Rydberg concluded that a clinical diagnosis in such cases was impossible.

Grulee (1936) reached practically the same conclusion in his study of 166 infants dying in the neonatal period, and in whom intracranial haemorrhage occurred in 20 He found that convulsions in the newborn could be a symptom of almost any disease.

Craig (1938) gave a detailed description of clinical observations and autopsy findings in 126 newborn infants dying of intracranial haemorrhage. The series was classified according to the site of the haemorrhage. As well as demonstrating aetiological differences within the respective categories he concluded. subarachnoidal haemorrhage gave usually rise either to unchar acteristic symptoms or to none at all (36 patients) Subdural haemorrhage, the most common finding (62 patients) often associated with tentorial tear

was characterized by a good period followed by an irritative stage and eventually by a depressive stage, whereas intraventricular haemorrhage followed a brief course with death concluding a sudden onset of severe symptoms, frequently associated with terminal hyperpyrexia. With haemorrhage into the brain substance the course was often lengthy with progressive weight loss, mental restlessness and pronounced physical weakness" More over it was stressed that convulsions were indicative of an intracranial process only in the presence of other symptoms of probable cerebral origin such as shrill cry or a bulging fontanelle. In the case of subdural haemorrhage convulsions were often more pronounced and of longer duration than in other forms of intracranial haemorrhage. Rigidity and opisthotonus were more indicative of intraventricular and subdural infratentorial haemorrhage; in the latter case this was usually associated with cyanosis in contrast to the former.

Bound, Butler and *Spector* (1956) published a survey of 211 consecutive neonatal deaths of mature and premature infants. The principal causes of death were: 1) intraventricular haemorrhage in 10 per cent, 2) intracranial birth injury in 18 per cent, 3) a "pulmonary syndrome in 27 per cent, 4) pneumonia in 12 per cent, 5) various diseases including malformations in 33 per cent. One or more of the following groups of symptoms were present in all the first four groups: 1) poor condition at birth, i.e. flaccidity and poor reaction to stimuli, cyanosis and respiratory irregularities—as seen in over half the cases in all four groups, 2) respiratory disorders in the form of rapid, irregular breathing, gradually with periods of apnoea, and intermittent or permanent cyanosis. These features were present in all the patients. 3) Irritative cerebral symptoms: convulsions, often associated with abnormal wakefulness, restlessness, irritability high-pitched cry and changes in tone. These last symptoms were seldom encountered in the absence of convulsions. Only 24 per cent of these patients had intracranial lesions and 63 per cent had pulmonary changes only —Just over one third of the patients with "pulmonary syndrome had irritative cerebral symptoms, and this also applied to the patients with intraventricular haemorrhage. One quarter of the patients with intracranial birth injury died within the first hour of life. Among the mature patients who lived longer the majority had irritative cerebral symptoms compared with less than half in the premature. It was concluded that the clinical picture was of no appreciable significance in the differential diagnosis.

Illingworth (1957) studied the significance of cyanotic attacks in the differential diagnosis in 170 newborn infants, 82, or 48 per cent of whom died neonatally 36 per cent of those had severe atelectases and 33 per cent had marked intracranial haemorrhage. Almost identical findings were present in newborn infants dying neonatally without having exhibited cyanotic attacks. Nineteen of those who did have cyanotic attacks also had convulsions. In

only in infratentorial haemorrhage, and apathy was more pronounced in intracranial haemorrhage. Tremor was as frequent in intracranial haemorrhage as in extracerebral conditions (atelectasis or infections) Convulsions were seen in only three of the newborn who died, none showing cerebral damage.

Catel (1932) and *Liebe* (1940) established the diagnosis of intracranial haemorrhage on the basis of differences in the bilirubin concentration in blood and spinal fluid and found the validity of this method confirmed by autopsy findings in 34 and 68 infants, respectively dying in the neonatal period. Both authors observed that some of the infants with intracranial haemorrhage failed to present any symptoms, and in patients with no intracranial haemorrhage similar symptoms might be observed as in those who had. They found, however that infants with intracranial haemorrhage frequently developed more symptoms but not enough to enable a diagnostic conclusion to be reached. Liebe regarded cyanosis, convulsions, refusal to nurse and decreased activity as non-specific symptoms, while delayed initial crying and intermittent loss of consciousness were more likely to be cerebral symptoms.

Rydberg (1932) observed that severe cerebral symptoms usually occurred after a symptomfree interval of hours or days poor nursing and apathy or intermittent or constant cyanosis as initial symptoms were followed by tremor rigidity convulsions irregular respiration and high-pitched cry All symptoms, however were inconsistent. With a full clinical picture they were considered almost pathognomonic of intracranial haemorrhage. Such a picture was observed in 34 infants who died in the neonatal period. Six of these had no intracranial haemorrhage, but prominent degenerative tissue alterations were present in the brain Rydberg further described an uncharacteristic picture, which also developed after a symptomfree interval and was seen in a variety of diseases. It consisted of irregular respiration and cyanosis Rydberg concluded that a clinical diagnosis in such cases was impossible.

Grulee (1936) reached practically the same conclusion in his study of 166 infants dying in the neonatal period, and in whom intracranial haemorrhage occurred in 20 He found that convulsions in the newborn could be a symptom of almost any disease.

Craig (1938) gave a detailed description of clinical observations and autopsy findings in 126 newborn infants dying of intracranial haemorrhage. The series was classified according to the site of the haemorrhage. As well as demonstrating aetiological differences within the respective categories he concluded, subarachnoidal haemorrhage gave usually rise either to uncharacteristic symptoms or to none at all (36 patients) Subdural haemorrhage, the most common finding (62 patients) often associated with tentorial tear

was characterized by a good period followed by an *irritative stage* and eventually by a depressive stage, whereas intraventricular haemorrhage followed a brief course with death concluding a *sudden onset of* severe symptoms, frequently associated with terminal hyperpyrexia. With haemorrhage into the brain substance the course was *often lengthy* with progressive weight loss, mental restlessness and pronounced "physical weakness" Moreover it was *stressed that convulsions* were indicative of an intracranial process *only in* the presence of other symptoms of probable cerebral origin *such as shrill cry* or a bulging fontanelle. In the case of subdural haemorrhage convulsions were often more pronounced and of longer duration than in *other forms* of intracranial haemorrhage. Rigidity and opisthotonus were more indicative of intraventricular and subdural infratentorial haemorrhage, in the latter case this was usually associated with cyanosis in contrast to the former

Bound, Butler and *Spector* (1956) published a survey of 211 consecutive neonatal deaths of mature and premature infants. The principal causes of death were: 1) intraventricular haemorrhage in 10 per cent, 2) intracranial birth injury in 18 per cent, 3) a "pulmonary syndrome" in 27 per cent, 4) pneumonia in 12 per cent, 5) various diseases including malformations in 33 per cent. One or more of the following groups of symptoms were present in all the first four groups: 1) poor condition at birth, i. e. flaccidity and poor reaction to stimuli, cyanosis and respiratory irregularities—as seen in *over half the cases in all four groups,* 2) *respiratory disorders in the form* of rapid, irregular breathing, gradually with periods of apnoea, and intermittent or permanent cyanosis. These *features* were present in all the patients. 3) Irritative cerebral symptoms: convulsions, often associated with abnormal wakefulness, restlessness, irritability high-pitched cry and changes in tone. These last symptoms were seldom encountered in the absence of convulsions. Only 24 per cent of these patients had intracranial lesions and 63 per cent had pulmonary changes only.—Just over one-third of the patients with "pulmonary syndrome" had irritative cerebral symptoms, and this also applied to the patients with intraventricular haemorrhage. One quarter of the patients with intracranial birth injury died within the first hour of life. Among the mature patients who *lived* longer the *majority had irritative* cerebral symptoms compared with less than half in the premature. It was concluded that the *clinical* picture was of no appreciable significance in the differential diagnosis.

Illingworth (1957) studied the significance *of* cyanotic attacks in the differential diagnosis in 170 newborn infants, 82, or 48 per cent of whom died neonatally. 36 per cent of those had severe atelectases and 33 *per cent* had marked intracranial haemorrhage. Almost identical findings were present in newborn infants dying neonatally without having exhibited cyanotic attacks. Nineteen of those who did have cyanotic attacks also had convulsions. In

eleven cases autopsy revealed intracranial abnormalities (haemorrhage or oedema) and in four atelectasis or congenital heart disease were disclosed.

Ahvenainen (1956 1957 1958 and 1959) carried out meticulous studies of the clinical and pathological findings in small groups of infants with either pulmonary or intracranial disorders who died in the neonatal period. He reported that cyanosis was among the most frequent symptoms in all groups. He also found that oxygen therapy often had no effect on cyanosis caused by cerebral damage Respiratory disorders were also common, and he considered irregular respiration to be the most reliable respiratory symptom in the diagnosis of intracranial conditions. Unconsciousness and flaccidity were more frequent than convulsions and rigidity in cerebral disorders. Though rare, all the cerebral symptoms might be present in pulmonary disorders convulsions were observed only in the terminal stage. Ahvenainen felt that the presence of two cerebral symptoms in any one patient made the diagnosis of intracranial disease more certain than one cerebral symptom He pointed out that pulmonary complications were frequent in intra cranial conditions and that their presence modified the cerebral symptoms, thus making the diagnosis even more difficult. He demonstrated that none of the features mentioned were common to all cases.

Peterman (1946) reported cerebral birth injury to be the cause of convulsions in 68 per cent of 176 infants with convulsions during the first month of life. Among other causes he mentioned acute infections within or outside the central nervous system, hydrocephalus cerebral agenesis and congenital heart disease. In 7 per cent of the cases the origin remained unknown.

Craig (1960) examined 374 infants with convulsions. 158 or 42 per cent died neonatally Postmortem examinations revealed a cerebral aetiology in 78 per cent. In 16 per cent only extracerebral disease was found, and in 6 per cent no cause could be discovered. He felt that convulsions could be distinguished to a certain extent according to aetiology Moreover he stated that severe cases of convulsion were remarkably rare in premature infants.

Dekaban in his book "Neurology of Infancy" (1959) described an essentially similar symptomatology in intracranial haemorrhage of varying localization as stated by *Craig* (1938)

In summarising, it may be concluded that the diagnosis of intracranial disease in the neonatal period has been considered difficult and has usually been established from the presence of one or more of the following symptoms cyanosis, respiratory disorders, abnormalities in consciousness and tone, convulsions and refusal to nurse The presence of several symptoms ensures a fairly accurate diagnosis. However where few symptoms are present—as is frequently the case—the diagnosis is extremely uncertain It would appear that no one symptom can be said to be specifically cerebral.

Previous studies on the prognosis of intracranial disorders in the newborn and the prognostic significance of neonatal symptoms

Brady (1918) found that among nine patients with severe cerebral symptoms four had died in the neonatal period from intracranial haemorrhage, three had survived, but with serious cerebral sequelae (spasticity and convulsions) and two had undergone a perfectly normal development.

Heidler (1927) published a follow-up study of fourteen out of 22 patients who had survived neonatal disease. All had had convulsions and several additional cerebral symptoms. At the age of three years 12 were found to be practically normal, two had hemiplegia, seizures and mental defects.

Dollinger (1927) found the prognosis of intracranial birth injury to be graver the earlier in onset, the longer duration and the more severe and numerous were the symptoms. Convulsions lasting longer than one day were invariably considered an ominous sign. The previously mentioned "large picture" implied a higher mortality rate, the "small picture" a lower mortality rate, though a higher morbidity.

Naujoks (1928) located 24 children who had survived a neonatal period characterized by severe cerebral symptoms. Nine, ranging from two to twenty years of age, were found to be perfectly normal, four had minor defects (macroencephaly "nervous stereotype" and speech disorders) which could not with certainty be related to birth injury. An unspecified number had died within the first year of life, several had mental defects, seizures and pareses of the legs, but no cases of Little's disease were found. No differences in neonatal symptomatology were demonstrated between those who were normal and those who had sequelae. However this had not been the object of the investigation.

Munro (1928 and 1930) analysed the symptoms in 117 newborn infants with suspected intracranial damage. Ignoring symptoms that had not been present in at least 10 patients, he distinguished between "major" symptoms, viz. those present in approximately one-half to well over two-thirds of the subjects, and "minor" symptoms, observed in around one-tenth to one-quarter only. This grouping had no relation to the prognostic significance of these symptoms, and severe symptoms were present in both groups. Cyanosis, which was common, was compatible with less than a 50 per-cent chance of survival, even less if associated with asphyxia or respiratory distress. With hypotonicity which was also very frequent, the rate of survival was more than 50 per cent. Irritative symptoms were rare (one-quarter of the patients) with 70 per-cent chance of survival. Among the rare symptoms, asphyxia, pallor and flaccidity implied a poor prognosis asphyxia was par

eleven cases autopsy revealed intracranial abnormalities (haemorrhage or oedema) and in four atelectasis or congenital heart disease were disclosed.

Ahvenainen (1956 1957 1958 and 1959) carried out meticulous studies of the clinical and pathological findings in small groups of infants with either pulmonary or intracranial disorders, who died in the neonatal period. He reported that cyanosis was among the most frequent symptoms in all groups. He also found that oxygen therapy often had no effect on cyanosis caused by cerebral damage. Respiratory disorders were also common and he considered irregular respiration to be the most reliable respiratory symptom in the diagnosis of intracranial conditions. Unconsciousness and flaccidity were more frequent than convulsions and rigidity in cerebral disorders. Though rare, all the cerebral symptoms might be present in pulmonary disorders convulsions were observed only in the terminal stage. Ahvenainen felt that the presence of two cerebral symptoms in any one patient made the diagnosis of intracranial disease more certain than one cerebral symptom He pointed out that pulmonary complications were frequent in intra cranial conditions and that their presence modified the cerebral symptoms, thus making the diagnosis even more difficult. He demonstrated that none of the features mentioned were common to all cases

Peterman (1946) reported cerebral birth injury to be the cause of convulsions in 68 per cent of 176 infants with convulsions during the first month of life. Among other causes he mentioned acute infections within or out side the central nervous system, hydrocephalus, cerebral agenesis and congenital heart disease. In 7 per cent of the cases the origin remained unknown.

Craig (1960) examined 374 infants with convulsions. 158 or 42 per cent died neonatally Postmortem examinations revealed a cerebral aetiology in 78 per cent. In 16 per cent only extracerebral disease was found, and in 6 per cent no cause could be discovered. He felt that convulsions could be distinguished to a certain extent according to aetiology Moreover he stated that severe cases of convulsion were remarkably rare in premature infants.

Dekaban in his book "Neurology of Infancy" (1959) described an essentially similar symptomatology in intracranial haemorrhage of varying localization as stated by *Craig* (1938)

In summarising, it may be concluded that the diagnosis of intracranial disease in the neonatal period has been considered difficult and has usually been established from the presence of one or more of the following symptoms cyanosis, respiratory disorders, abnormalities in consciousness and tone, convulsions and refusal to nurse. The presence of several symptoms ensures a fairly accurate diagnosis. However where few symptoms are present—as is frequently the case—the diagnosis is extremely uncertain. It would appear that no one symptom can be said to be specifically cerebral.

Previous studies on the prognosis of intracranial disorders in the newborn and the prognostic significance of neonatal symptoms

Brady (1918) found that among nine patients with severe cerebral symptoms four had died in the neonatal period from intracranial haemorrhage, three had survived, but with serious cerebral sequelae (spasticity and convulsions) and two had undergone a perfectly normal development.

Heddler (1927) published a follow-up study of fourteen out of 22 patients who had survived neonatal disease. All had had convulsions and several additional cerebral symptoms. At the age of three years 12 were found to be practically normal, two had hemiplegia, seizures and mental defects.

Dollinger (1927) found the prognosis of intracranial birth injury to be graver the earlier in onset, the longer duration and the more severe and numerous were the symptoms. Convulsions lasting longer than one day were invariably considered an ominous sign. The previously mentioned "large picture" implied a higher mortality rate, the "small picture" a lower mortality rate, though a higher morbidity.

Naujoks (1928) located 24 children who had survived a neonatal period characterized by severe cerebral symptoms. Nine, ranging from two to twenty years of age, were found to be perfectly normal, four had minor defects (macroencephaly nervous stereotype" and speech disorders) which could not with certainty be related to birth injury An unspecified number had died within the first year of life; several had mental defects, seizures and pareses of the legs, but no cases of Little's disease were found. No differences in neonatal symptomatology were demonstrated between those who were normal and those who had sequelae. However this had not been the object of the investigation.

Munro (1928 and 1930) analyzed the symptoms in 117 newborn infants with suspected intracranial damage. Ignoring symptoms that had not been present in at least 10 patients, he distinguished between "major" symptoms, viz. those present in approximately one-half to well over two-thirds of the subjects, and "minor" symptoms, observed in around one-tenth to one-quarter only This grouping had no relation to the prognostic significance of these symptoms, and severe symptoms were present in both groups. Cyanosis, which was common, was compatible with less than a 50 per-cent chance of survival, even less if associated with asphyxia or respiratory distress. With hypotonicity which was also very frequent, the rate of survival was more than 50 per cent. Irritative symptoms were rare (one-quarter of the patients) with 70 per-cent chance of survival. Among the rare symptoms, asphyxia, pallor and flaccidity implied a poor prognosis, asphyxia was par

eleven cases autopsy revealed intracranial abnormalities (haemorrhage or oedema) and in four atelectasis or congenital heart disease were disclosed.

Ahvenainen (1956 1957 1958 and 1959) carried out meticulous studies of the clinical and pathological findings in small groups of infants with either pulmonary or intracranial disorders, who died in the neonatal period. He reported that cyanosis was among the most frequent symptoms in all groups. He also found that oxygen therapy often had no effect on cyanosis caused by cerebral damage Respiratory disorders were also common, and he considered irregular respiration to be the most reliable respiratory symptom in the diagnosis of intracranial conditions. Unconsciousness and flaccidity were more frequent than convulsions and rigidity in cerebral disorders. Though rare, all the cerebral symptoms might be present in pulmonary disorders convulsions were observed only in the terminal stage. Ahvenainen felt that the presence of two cerebral symptoms in any one patient made the diagnosis of intracranial disease more certain than one cerebral symptom. He pointed out that pulmonary complications were frequent in intracranial conditions and that their presence modified the cerebral symptoms, thus making the diagnosis even more difficult. He demonstrated that none of the features mentioned were common to all cases.

Peterman (1946) reported cerebral birth injury to be the cause of convulsions in 68 per cent of 176 infants with convulsions during the first month of life. Among other causes he mentioned acute infections within or out side the central nervous system, hydrocephalus, cerebral agenesis and congenital heart disease. In 7 per cent of the cases the origin remained unknown.

Craig (1960) examined 374 infants with convulsions. 158 or 42 per cent died neonatally Postmortem examinations revealed a cerebral aetiology in 78 per cent. In 16 per cent only extracerebral disease was found, and in 6 per cent no cause could be discovered He felt that convulsions could be distinguished to a certain extent according to aetiology Moreover he stated that severe cases of convulsion were remarkably rare in premature infants.

Dekaban in his book "Neurology of Infancy" (1959) described an essentially similar symptomatology in intracranial haemorrhage of varying localization as stated by *Craig* (1938)

In summarising, it may be concluded that the diagnosis of intracranial disease in the neonatal period has been considered difficult and has usually been established from the presence of one or more of the following symptoms cyanosis, respiratory disorders, abnormalities in consciousness and tone, convulsions and refusal to nurse. The presence of several symptoms ensures a fairly accurate diagnosis. However where few symptoms are present—as is frequently the case—the diagnosis is extremely uncertain. It would appear that no one symptom can be said to be specifically cerebral.

had been practically identical in the neonatal period (cf. page 14). The follow-up also failed to reveal any differences. Three, or 21 per cent, of Liebe's fourteen patients with intracranial haemorrhage and sixteen (24 per cent) of 68 patients without intracranial haemorrhage had severe cerebral sequelae. The corresponding figures in Catel's somewhat smaller series were 33 and 25 per cent, respectively.

Craig (1950) published an extensive and detailed study on 593 children with neonatal intracranial irritation. He had excluded children with morbus haemolyticus neonatorum, severe persistent atelectasis and malformations. The series was divided into five groups according to neonatal symptom groups in decreasing degrees of severity. All the children had been seen at the age of six months. 12 patients were excluded because of microcephaly and handicaps that might be of hereditary developmental origin or acquired at a later date. 14 per cent were not re-examined after 6 months of age, 6 per cent died of unknown causes, 80 per cent were followed up until the age of one year. 71 per cent to the age of three years and 52 per cent beyond five years of age. In the entire material severe cerebral sequelae were present in 56, or 9 per cent. In the group with severe neonatal symptoms (53 patients) sequelae were found in 21 per cent, in the group with pronounced symptoms (104 patients) in 10 per cent, in the group with moderate symptoms (238 patients) in 8 per cent, of those with mild symptoms (187 patients) 7 per cent had sequelae, and for those with delayed symptoms (11 patients) the rate was 36 per cent.—The patients with severe sequelae were fairly evenly distributed throughout the symptomatological groups.—Craig concluded that there was no correlation between neonatal symptoms and later development except in cases with delayed neonatal symptoms, which gave a poor prognosis. The outlook for immediate survival was grim in the presence of collapse, gasping and irregular respiration that was not corrected within hours, particularly when associated with cyanosis. A marked difference in the symptomatology of premature and mature infants was demonstrated by Craig in so far as the premature only rarely showed the violent clinical pictures in the neonatal period. If convulsions occurred in the premature, the prognosis for survival was grave. However the late prognosis was no worse for premature patients than for mature. It was suggested that it was the duration of the neonatal symptoms rather than their severity that was prognostically significant.

Roudinesco, Tardieu, Willwald and *Trelat* (1951) followed up throughout a period of three years 54 out of 62 children who had been admitted to hospital in the neonatal period because of suspected cerebral disease. 60 per cent developed normally. 25 per cent had permanent cerebral sequelae of varying degrees and 15 per cent seemed to have been only temporarily retarded. Symptoms with grave prognostic implications were in this study so-

ticularly relevant to late sequelae. Common symptoms were also feeble crying, poor nursing, apathy respiratory disorders and a bulging fontanelle. Half the 117 patients died in the neonatal period. 48 of the 58 survivors were included in the follow-up at ages varying from 2$^1/_2$ to 7 years. 34 (70 per cent) were found to be normal and 7 (14 per cent) had serious cerebral sequelae. Of these four had died an additional seven deaths were due to extracranial causes Munro did not differentiate the neonatal symptomatology in the various groups of survivors.

Fleming and Morton (1930) in a comparable study investigated a series of 103 patients with neonatal symptoms interpreted as cerebral in origin. They too found that about half the patients had died. Out of 53 survivors 33 were examined at the age of at least one year Of these 28 or 85 per cent, were normal and 5 or 15 per cent, had severe cerebral defects. At least seven were reported to have died after the neonatal period, however the cause of death could not be established. Fleming found no differences in the neonatal symptomatology between those who were eventually found to be normal and those who had sequelae. He concluded that it was impossible to predict the outcome of the survivors. Cyanotic attacks and convulsions were considered to be specific cerebral symptoms. Convulsions occurred in about half the patients their chance of survival equalled that of Munro's patients with irritative cerebral symptoms.

Rydberg (1932) reported a graver prognosis in 48 children surviving severe neonatal symptoms. One third developed severe cerebral sequelae, approximately a further third had obvious cerebral symptoms. The final prognosis of the latter however was uncertain. But one-third were normal or practically normal. The age range of the children at follow-up was three to eighteen years. No differences in symptomatology could be demonstrated in the respective groups.

Fischer (1938) investigated a series similar to that of *Heidler*'s (1927) comprising 24 children who had had convulsions and various other cerebral symptoms in the neonatal period. 18 were traced and re-examined. The outlook was worse than in Heidler's series, with five deaths from cerebral causes presumably related to the neonatal disease. Five had varying degrees of mental handicap Two of these also had convulsions, two had speech disorders and one had impaired hearing. Eight, or 44 per cent, were found to be normal.

Catel (1933) and *Liebe* (1940) who based the diagnosis of intracranial haemorrhage primarily on the relationship between bilirubin levels in blood and spinal fluid carried out follow-up studies on two series of 26 and 82 children, respectively who had survived neonatal disease. Both series included children in whom intracranial haemorrhage had been diagnosed, and others in whom the diagnosis had been disproved. Clinically the two groups

had been practically identical in the neonatal period (cf. page 14). The *follow-up* also failed to reveal any differences. Three, or 21 per cent, of Liebe's fourteen patients with intracranial haemorrhage and sixteen (24 per cent) of 68 patients without intracranial haemorrhage had severe cerebral sequelae. The corresponding figures in Catel's somewhat smaller series were 33 and 25 per cent, respectively.

Craig (1950) published an extensive and detailed study on 593 children with neonatal intracranial irritation. He had excluded children with morbus haemolyticus neonatorum, severe persistent atelectasis and malformations. The series was divided into five groups according to neonatal symptom groups in decreasing degrees of severity. All the children had been seen at the age of six months. 12 patients were excluded because of microcephaly and handicaps that might be of hereditary developmental origin or acquired at a later date. 14 per cent were not re-examined after 6 months of age, 6 per cent died of unknown causes, 80 per cent were followed up until the age of one year. 71 per cent to the age of three years and 52 per cent beyond five years of age. In the entire material severe cerebral sequelae were present in 56, or 9 per cent. In the group with severe neonatal symptoms (53 patients) sequelae were found in 21 per cent, in the group with pronounced symptoms (104 patients) in 10 per cent, in the group with moderate symptoms (238 patients) in 8 per cent, of those with mild symptoms (187 patients) 7 per cent had sequelae, and for those with delayed symptoms (11 patients) the rate was 36 per cent.—The patients with severe sequelae were fairly evenly distributed throughout the symptomatological groups.—Craig concluded that there was no correlation between neonatal symptoms and later development except in cases with delayed neonatal symptoms, which gave a poor prognosis. The outlook for immediate survival was grim in the presence of collapse, gasping and irregular respiration that was not corrected within hours, particularly when associated with cyanosis. A marked difference in the symptomatology of premature and mature infants was demonstrated by Craig in so far as the premature only rarely showed the violent clinical pictures in the neonatal period. If convulsions occurred in the premature, the prognosis for survival was grave. However the late prognosis was no worse for premature patients than for mature. It was suggested that it was the duration of the neonatal symptoms rather than their severity that was prognostically significant.

Roudinesco Tardieu Willwald and *Trelat* (1951) followed up throughout a period of three years 54 out of 62 children who had been admitted to hospital in the neonatal period because of suspected cerebral disease. 60 per cent developed *normally* 25 per cent had permanent cerebral sequelae of varying degrees and 15 per cent seemed to have been only temporarily retarded. Symptoms with grave prognostic implications were in this study se-

were primary asphyxia and flaccidity (which was rare) cyanosis was a somewhat less, though *still serious* prognostic sign, whereas hypertonicity was found to be of minor importance, and convulsions even less.

Hellström and *Jonsson* (1953) investigated 85 full term infants, who had been admitted to a paediatric ward either because of asphyxia or with manifest signs of oxygen *deficit or* evidence of intracranial haemorrhage. 18 died in the neonatal period of these 15 had intracranial haemorrhage. Four died later of unknown causes The remaining 63 were examined at ages ranging from 2 to 9 *years* 28 per cent had severe sequelae. Not all these children had shown clinical symptoms in the neonatal period. Cyanosis, which occurred in 40 per cent, and hypotonicity present in 17 per cent, were found to have no significance in the late prognosis. Convulsions and rigidity occurring in 15 per cent, seemed to imply a poor prognosis, since about 80 per cent of the patients in whom these symptoms were observed *later developed* severe sequelae. In contrast, only 20 per cent of the children who had had none of these symptoms were found to have sequelae.

Znamenacek Horsky Jirsova and *Melichar* (1957) followed up 202 children having had evidence of perinatal injury until the age of 3 years. A large majority (167) had presented symptoms only within the first day of *life (ascribed* to postnatal aspiration, asphyxia—often severe—anaesthesia or traumatic shock) The fact that all these children later developed normally implies that symptoms lasting up to 24 hours may be considered unimportant.—26 had symptoms of up to ten days duration The symptoms were graduaded as mild (rigidity transient irritability opisthotonus and tremor in mature infants and brief spells of apnoe and cyanosis in the premature) and severe (pronounced depressive and irritative symptoms) The mild symptoms left no sequelae in the severe cases sequelae in the form of retarded development were found in 5 out of 15 cases. Great prognostic significance was ascribed to convulsions unconsciousness and insufficient response to stimuli in the full term infants and, in the premature, their failure to maintain normal breathing.

Gross (1958) in a follow-up study of 136 children presenting various cerebral symptoms neonatally found that 6 per cent had died of unknown causes, 11 per cent had serious cerebral sequelae, and 83 per cent were perfectly normal. The ages at follow-up were from one to seven years and the follow-up percentage was 58 Gross found that cerebral symptoms were not necessarily unfavourable prognostic signs.

Burke (1954) examined a series of 46 newborn infants with special regard to the prognostic significance of convulsions. 18 or 38 per cent, died in the neonatal period. The prognosis for immediate survival appeared to be appreciably worse in the premature, with six out of 10 patients dying, while only 12 out of 36 mature infants had died. Among the survivors, 5 (19

per cent) developed severe cerebral sequelae, comparable to the rate found by *Heidler* (1927)

Bound, Butler and *Spector* (1956) found convulsions to be a grave prognostic sign for immediate survival, particularly in the premature, in whom, as mentioned on page 15 this symptom is rare. Out of 24 full-term infants with convulsions 42 per cent died neonatally compared with 79 per cent of 33 premature.

Craig (1960) in his paper on convulsions during the first 10 days of life, reported a follow-up study of 141 out of 152 children with neonatal convulsions of probable cerebral origin compared with 488 children who had had no convulsions, but other evidence of postnatal anoxia. The age at follow-up was well over three years. He found a higher incidence of severe cerebral sequelae (8 per cent) in the group with convulsions than in the group with none (3 per cent) The duration of the convulsions apparently had no effect on the outcome.

Harlem and *Oxeid* (1961) attached great importance to convulsions, especially when occuring repeatedly during the neonatal period. They followed-up 189 children who had various symptoms of cerebral irritation (immediate mortality rate 50 per cent) and found sequelae in 33 per cent.

Ford (1960) pointed out that little is known of the anatomical conditions in the brains of children surviving a perinatal injury He felt that numerous disorders have been ascribed to birth injury without conclusive evidence and he emphasized that even those best able to express an opinion on the subject appear to disagree.

To sum up, one must admit that there is basis for dispute. There is, however general agreement that a prognosis based on clinical observations only is precarious, indeed. Opinions differ also concerning the relative prognostic significance of individual symptoms, and to a lesser degree as to the future development of children with supposed cerebral symptoms in the neonatal period.

Recent years have brought forth new and more systematic methods of investigation. In 1953 Apgar presented her method for evaluating the condition of newborn infants within minutes of birth. Her scoring system, by which heartbeat, respiration, muscle tone, reflex irritability and colour were recorded and classified, the highest score indicating the optimal condition, has been widely used and has proved its validity It has revealed a close correlation between low scores and high neonatal mortality especially within the first two days of life. The correlation was more apparent with low scores at five minutes than at one minute after birth, and the highest mortality was found in infants with low birth weights and low scores (*Drage Kennedy* and *Schwar*~ 1964) Apgar's system has also proved of prognostic value with regard to later morbidity A considerable number of neurological defects

vere primary asphyxia and flaccidity (which was rare) cyanosis was a somewhat less, though still serious prognostic sign, whereas hypertonicity was found to be of minor importance, and convulsions even less.

Hellström and *Jonsson* (1953) investigated 85 full-term infants, who had been admitted to a paediatric ward either because of asphyxia or with manifest signs of oxygen deficit or evidence of intracranial haemorrhage. 18 died in the neonatal period of these 15 had intracranial haemorrhage. Four died later of unknown causes. The remaining 63 were examined at ages ranging from 2 to 9 years 28 per cent had severe sequelae. Not all these children had shown clinical symptoms in the neonatal period. Cyanosis, which occurred in 40 per cent, and hypotonicity present in 17 per cent, were found to have no significance in the late prognosis. Convulsions and rigidity occurring in 15 per cent, seemed to imply a poor prognosis, since about 80 per cent of the patients in whom these symptoms were observed later developed severe sequelae. In contrast, only 20 per cent of the children who had had none of these symptoms were found to have sequelae.

Znamenacek Horsky Jirsova and *Melichar* (1957) followed up 202 children having had evidence of perinatal injury until the age of 3 years. A large majority (167) had presented symptoms only within the first day of life (ascribed to postnatal aspiration, asphyxia—often severe—anaesthesia or traumatic shock) The fact that all these children later developed normally implies that symptoms lasting up to 24 hours may be considered unimportant.—26 had symptoms of up to ten days duration. The symptoms were graduaded as mild (rigidity transient irritability opisthotonus and tremor in mature infants and brief spells of apnoe and cyanosis in the premature) and severe (pronounced depressive and irritative symptoms) The mild symptoms left no sequelae in the severe cases sequelae in the form of retarded development were found in 5 out of 15 cases. Great prognostic significance was ascribed to convulsions, unconsciousness and insufficient response to stimuli in the full term infants and, in the premature, their failure to maintain normal breathing.

Gross (1958) in a follow up study of 136 children presenting various cerebral symptoms neonatally found that 6 per cent had died of unknown causes, 11 per cent had serious cerebral sequelae, and 83 per cent were perfectly normal. The ages at follow-up were from one to seven years and the follow up percentage was 58 Gross found that cerebral symptoms were not necessarily unfavourable prognostic signs.

Burke (1954) examined a series of 46 newborn infants with special regard to the prognostic significance of convulsions 18 or 38 per cent, died in the neonatal period. The prognosis for immediate survival appeared to be appreciably worse in the premature, with six out of 10 patients dying, while only 12 out of 36 mature infants had died. Among the survivors, 5 (19

CHAPTER II

Material and method

The present series consists of 291 children who, in the neonatal period, have been admitted to a paediatric ward because of symptoms suggesting cerebral damage.

The infants had been admitted to the Department of Paediatrics (DPGe) at Copenhagen County Hospital in Gentofte (KASGe) over a ten-year period (1946–1955) Although the neonatal period is defined here as the first week of life, a number of patients who were admitted during their second week have been included, they had, however, exhibited symptoms during the first week of life.

The investigation is based on the hospital records, and the patients were selected as follows: All cases that were registered under a diagnosis of intracranial haemorrhage, a total of 156 have been included. A review of the records revealed that the diagnosis had been based on the following symptoms, occurring in varying combinations and numbers, seldom alone, in the following order of frequency-

1) cyanosis, mostly attackwise, though in several cases constant. (Peripheral cyanosis has been disregarded)
2) Respiratory disorders consisting of irregular often difficult, grunting respiration, occasionally with periodic apnea.
3) hypotonicity often combined with apathy
4) Convulsions.
5) Tremor
6) Restlessness and irritability
7) Rigidity

It was apparent from the records that the diagnosis in several cases had been based on 1–3 of the following symptoms. cyanosis, respiratory disorders and apathy none of which can be considered specifically cerebral in nature.

The file was therefore searched for diagnoses that either a) suggested cerebral damage (difficult delivery skull fracture, asphyxia neonatorum), or

were found at the age of one year in children with low scores, again most apparent with five minutes low scores, and the worst prognosis was found in small premature infants with low scores (*Drage* and *Berendes* 1966) Their results have been published as part of a comprehensive collaborative study on cerebral palsy mental deficiency and other neurological disorders in childhood.

Graham Matarazzo and *Caldwell* (1956) published another method for the evaluation of the newborn, which they used in 265 newborn infants with no perinatal complications and in 81 with anoxic or cerebral complications, and correlated with re-examination of the children at the age of 3 years (*Graham Ernhart Thurston* and *Craft* 1962) A higher incidence of sequelae was revealed in those children who had been suspected of cerebral defects neonatally but there was no consistent parallel between the neonatal tests and the later condition, although certain significant correlations were established.

A very elaborate method for neurological examination on the basis of observation of the development of the central nervous system and its mode of reaction in childhood has been developed by *André Thomas* and *Saint-Anne Dargassies* (1952) *Prechtl* (1956 and 1964) *Prechtl* and *Dijkstra* (1959) The object has been the disclosure of minor brain damage in the neonatal period. The prognostic significance of the abnormal neurological findings in neonates was confirmed by follow up studies (*Prechtl* 1960 *Dijkstra* 1960 *Smithells* 1961 and *Saint Anne Dargassies* 1962) which disclosed significantly more neurological disorders, especially behaviour deviations, in the groups with abnormalities in the neonatal period as compared with normal neonates These methods are extremely time-consuming and require great experience, if errors of judgment are to be avoided This has been stressed by *Illingworth* (1960) among others, who anticipated the risk of demonstrating in the newborn more and more signs that will eventually disappear *Paine* (1960) also questioned the prognostic value of some of these elaborate investigations and stressed his point again (*Donovan Coues* and *Paine* 1962) in a paper on 192 full-term infants observed at birth and again at the age of one year He concluded that conventional neurological signs and infantile postural automatisms were of limited prognostic value, even though "minimal brain damage" could not be expected to be disclosed at the age of one year However the investigations were found to be useful in the neonatal diagnosis —The methods are widely used at present, where large prospective studies are in progress, and the final judgment must be withheld until the completion of a long-term follow-up study

Follow-up examination

At the follow-up examination the mothers were interviewed in order to obtain supplementary data concerning pregnancy and delivery and a detailed history of the children was taken. Special emphasis was placed on general condition and growth during the first years of life as well as later. An attempt was made to assess whether the motor and mental development of the patients had differed from the assumed average. With older normal children it could be difficult to assess the exact time at which a child had mastered such important functions as walking, talking or toilet habits. Had development not been unsatisfactory information was generally more accurate.

In younger children the mental state was assessed by information about their ability to play or amuse themselves, to get along with other children, especially of their own age, and about their interest in their environment. If the children were older the mothers were asked at what age the children had begun school and what progress they had made there.

When behaviour problems were present, the nature of the defect was explored as far as possible, and an attempt was made to disclose possible causative factors in the child's environment.

If psychological testing had been carried out, either because of a suspected mental defect or specific difficulties with learning or behaviour problems, reports were obtained from doctors or psychologists. In only a few cases had psychological tests been brought about with the prime object of assessing whether a so-called organic element was present or not.

During the examination of the child no proper psychological tests were made however a clinical evaluation was made, based on conversation with the child and observation during the examination itself, which usually lasted for about an hour

Electroencephalography (EEG) was performed wherever possible in cases where deviations of behaviour were suspected to be of organic origin. The recordings were performed and interpreted by the physicians of the EEG-laboratory at the University Clinic of Paediatrics.

A number of the children, who had a present or past history of various types of seizures, were, when possible, examined by EEG. If this had not already been done. If EEG studies had already been made, the reports were obtained.

In the same way data on previous examinations were obtained, if the child had been seen by specialists because of defects of vision, hearing or speech, or if a disorder of assumed cerebral origin had led to admission to hospital or out-patient treatment.

Finally a general physical and neurological examination was performed.

b) suggested the presence of the above-mentioned non specific symptoms (pulmonary atelectasis, aspiration into the lungs or congenital debility) From these two groups have been selected those infants who presented at least two of the non-specific or at least one of the presumably specific symptoms, from a) 31 from b) 104 patients.

Infants who might have exhibited similar symptoms, but were registered under other definite diagnoses, such as proven heart disease or hiatus hernia, were omitted So were patients with icterus neonatorum with or without blood-group-incompatibility

As with any other study based on records that have not been written with a specific scientific objective in mind, to a certain extent the present material must be considered unreliable. One should be able to rely upon notes stating the presence or absence of a symptom however one is at a loss if the symptom is not mentioned at all

From this point, when a symptom is said to have been absent, in some instances this may have been stated explicitly in other cases, however the symptom may not have been mentioned in the notes No such distinction has been made in the analysis of the material on the assumption that a serious symptom would have been recorded, had it been present.

Information about pregnancy and delivery is more unsatisfactory since all the infants had been delivered at a place other than the KASGe (at home, in a private clinic or at another hospital) The data accompanying the child on admission was often scanty and additional information was not always obtainable.

Cases in which a given procedure has not been mentioned and those where it was explicitly stated that the procedure had not been applied have therefore not been listed together

The following information has been extracted from the records.

1) *Data on the mother* Age, parity matrimonial status, condition during pregnancy and complications, if any
2) *Data on the delivery* Course and duration, complications, use of labour stimulating methods morphin, or forceps.
3) *Data on the patient.* If asphyxia occurred its duration as well as the extent and method of attempted resuscitation. (In the present study asphyxia is defined as delayed establishment of spontaneous respiration after birth) The age of the child on admission to the ward and the duration of the admission. The symptoms that caused the admission or developed following admission. The time of onset and the duration of these symptoms. The therapy applied. The condition of the infant at discharge. Where death occurred, extracts from the autopsy report were obtained.

Follow-up examination

At the follow-up examination the mothers were interviewed in order to obtain supplementary data concerning pregnancy and delivery and a detailed history of the children was taken. Special emphasis was placed on general condition and growth during the first years of life as well as later. An attempt was made to assess whether the motor and mental development of the patients had differed from the assumed average. With older normal children it could be difficult to assess the exact time at which a child had mastered such important functions as walking, talking or toilet habits. Had development not been unsatisfactory, information was generally more accurate.

In younger children the mental state was assessed by information about their ability to play or amuse themselves, to get along with other children, especially of their own age, and about their interest in their environment. If the children were older, the mothers were asked at what age the children had begun school and what progress they had made there.

When behaviour problems were present, the nature of the defect was explored as far as possible, and an attempt was made to disclose possible causative factors in the child's environment.

If psychological testing had been carried out, either because of a suspected mental defect or specific difficulties with learning or behaviour problems, reports were obtained from doctors or psychologists. In only a few cases had psychological tests been brought about with the prime object of assessing whether a so-called organic element was present or not.

During the examination of the child no proper psychological tests were made, however, a clinical evaluation was made, based on conversation with the child and observation during the examination itself, which usually lasted for about an hour.

Electroencephalography (EEG) was performed wherever possible in cases where deviations of behaviour were suspected to be of organic origin. The recordings were performed and interpreted by the physicians of the EEG-laboratory at the University Clinic of Paediatrics.

A number of the children, who had a present or past history of various types of seizures, were, when possible, examined by EEG if this had not already been done. If EEG studies had already been made, the reports were obtained.

In the same way data on previous examinations were obtained, if the child had been seen by specialists because of defects of vision, hearing or speech, or if a disorder of assumed cerebral origin had led to admission to hospital or out-patient treatment.

Finally, a general physical and neurological examination was performed.

b) suggested the presence of the above-mentioned non specific symptoms (pulmonary atelectasis, aspiration into the lungs or congenital debility) From these two groups have been selected those infants who presented at least two of the non specific or at least one of the presumably specific symptoms from a) 31 from b) 104 patients

Infants who might have exhibited similar symptoms, but were registered under other definite diagnoses, such as proven heart disease or hiatus hernia, were omitted So were patients with icterus neonatorum, with or without blood-group-incompatibility

As with any other study based on records that have not been written with a specific scientific objective in mind to a certain extent the present material must be considered unreliable. One should be able to rely upon notes stating the presence or absence of a symptom however one is at a loss if the symptom is not mentioned at all

From this point, when a symptom is said to have been absent, in some instances this may have been stated explicitly in other cases, however the symptom may not have been mentioned in the notes. No such distinction has been made in the analysis of the material on the assumption that a serious symptom would have been recorded, had it been present.

Information about pregnancy and delivery is more unsatisfactory since all the infants had been delivered at a place other than the KASGe (at home, in a private clinic or at another hospital) The data accompanying the child on admission was often scanty and additional information was not always obtainable.

Cases in which a given procedure has not been mentioned and those where it was explicitly stated that the procedure had not been applied have therefore not been listed together

The following information has been extracted from the records.

1) *Data on the mother* Age, parity matrimonial status, condition during pregnancy and complications, if any
2) *Data on the delivery* Course and duration complications, use of labour-stimulating methods morphia, or forceps.
3) *Data on the patient.* If asphyxia occurred its duration as well as the extent and method of attempted resuscitation (In the present study asphyxia is defined as delayed establishment of spontaneous respiration after birth) The age of the child on admission to the ward and the duration of the admission The symptoms that caused the admission or developed following admission. The time of onset and the duration of these symptoms. The therapy applied The condition of the infant at discharge. Where death occurred, extracts from the autopsy report were obtained.

Follow-up examination

At the *follow-up examination* the mothers were interviewed in order to obtain supplementary data concerning pregnancy and delivery and a detailed history of the children was taken. Special emphasis was placed on general condition and growth during the first years of life as well as later An attempt was made to assess whether the motor and mental development of the patients had differed from the assumed average. With older normal children it could be difficult to assess the exact time at which a child had mastered such important functions as walking, talking or toilet habits. Had development not been unsatisfactory information was generally more accurate.

In younger children the mental state was assessed by information about their ability to play or amuse themselves, to get along with other children, especially of their own age, and about their interest in their environment. If the children were older the mothers were asked at what age the children had begun school and what progress they had made there.

When behaviour problems were present, the nature of the defect was explored as far as possible, and an attempt was made to disclose possible causative factors in the child's environment.

If psychological testing had been carried out, either because of a suspected mental defect or specific difficulties with learning or behaviour problems, reports were obtained from doctors or psychologists. In only a few cases had psychological tests been brought about with the prime object of assessing whether a so-called organic element was present or not.

During the examination of the child no proper psychological tests were made- however a clinical evaluation was made, based on conversation with the child and observation during the examination itself, which usually lasted for about an hour

Electroencephalography (EEG) was performed wherever possible in cases where deviations of behaviour were suspected to be of organic origin. The recordings were performed and interpreted by the physicians of the EEG-laboratory at the University Clinic of Paediatrics.

A number of the children, who had a present or past history of various types of seizures, were, when possible, examined by EEG if this had not already been done. If EEG studies had already been made, the reports were obtained.

In the same way data on previous examinations were obtained, if the child had been seen by specialists because of defects of vision, hearing or speech, or if a disorder of assumed cerebral origin had led to admission to hospital or out-patient treatment.

Finally a general physical and neurological examination was performed.

The follow-up study was begun at the end of 1958 at that time the children were thus between three and thirteen years old.

Of the total of 291 children 123 had died during their first admission to hospital. Autopsy had been performed in all cases but one (owing to refusal by the parents) and this case has been excluded from the material.

168 patients survived the neonatal period. Of these 15 had to be ex cluded. four could not be traced four had left the country and their ad dresses were unobtainable the parents of five refused to cooperate and data about these children were unobtainable in any other way one infant had died with the mother from carbon monoxide poisoning. The death certificate carried no additional information. One child who had athetosis, was excluded because she was later found to have had prolonged jaundice due to blood-group-incompatibility between mother and child.

12 infants, who had died at a later date, have been included in the ma terial since there was ample information about their subsequent history· in seven cases autopsy reports were available. In the case of six of the survivors it was possible to obtain written information only

The remaining children have been examined either at the DPGo follow ing written invitation, in their homes or at the institutions in which they had been placed.

This gives a follow-up percentage, among the survivors, of 91 For the entire series, now reduced to 275 cases, the percentage is 95

The neonatal symptoms

As mentioned above, the neonatal symptoms related to cerebral damage or cerebral irritation were as follows cyanosis, respiratory disorders, hypotonicity convulsions, tremor irritability and rigidity

Fig. 1 a shows the incidence of each of the neonatal symptoms. It will be seen that three-quarters of the patients had cyanosis, well over one-half had respiratory abnormalities and apathy less than a quarter had convulsions and less than one fifth had tremor irritability and rigidity There was an average of 2.5 symptoms per patient. Because of the origin of the material it should be permissible to regard these figures as minimum numbers.

37 or 13 per cent of the patients had exhibited only one symptom. 22 had cyanosis, 8 hypotonicity 3 respiratory disorders, 2 convulsions and 2 irritability The remainder had exhibited symptoms in varying combinations.

The rate of prematurity in the total material was very high 96 infants, or 35 per cent, had a birth weight (BW) below 2500 grams. The available information on the length of gestation did not permit classification and the distinction between maturity and prematurity therefore had to be based on

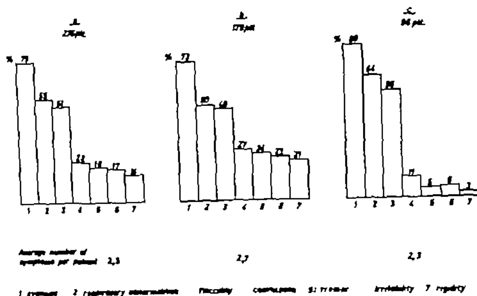


Fig. 1

Incidence of the neonatal symptoms: a) in the total material, b) in patients with BWs over 2500 grams and c) in patients with BWs below 2500 grams.

the BW alone.—As the premature might be expected to show a different pattern from that of the mature, the following analysis of the material is made also for the two weight groups separately

Fig. 1 b and c illustrate the incidence of neonatal symptoms in mature and premature patients, respectively It reveals a trend towards a higher incidence of cyanosis, respiratory disorders and flaccidity in the premature and a somewhat more pronounced tendency towards higher occurrence of convulsions, tremor irritability and rigidity in the mature. Moreover there is a faint tendency for the mature to exhibit more symptoms than the premature: respectively 2.7 and 2.3 symptoms per patient.

Results of the follow-up

Of the 75 patients 44 per cent had died during the neonatal period, 11 per cent developed severe cerebral defects, 9 per cent had minor cerebral sequelae; 11 per cent, though essentially normal, had various minor abnormalities that, with a degree of certainty could be traced to the neonatal

The diagnoses of each group will be dealt with in details as follows.

1 Patients dying in the neonatal period

As mentioned above, autopsy including brain section, had been performed on all 122 patients. The studies were performed in the Department of Pathology of the KASGe. In Table 1 the principal findings are listed for the entire group, as well as for mature and premature patients.

Atelectasis was the most frequent finding and, as might be expected, more frequent in the premature. In all cases there were widespread pulmonary changes. Next in frequency were intracranial haemorrhages, somewhat commoner in the mature than in the premature. Tentorial tear was the predominant brain lesion in both weight groups, though much more frequent

TABLE 1

Principal autopsy findings in 122 patients dying in the neonatal period

	BW $\geq$ 2500 gm 55 pat.	BW $\leq$ 2500 gm 67 pat.	Total 122 pat.
Pulmonary atelectasis	75 %	88 %	81 %
Intracranial haemorrhage	73 %	63 %	67 %
Tentorial tear	64 %	48 %	55 %
Rupture of falx	[illegible] %	3 %	2 %
Intraventric. haemorrhage	5 %	6 %	6 %
Rupture of sagittal sinus	2 %	0	1 %
Subdural haemorrhage	4 %	3 %	3 %
Subarachnoidal haemorrhage	4 %	2 %	2 %
Meningeal haemorrhage	13 %	10 %	11 %
Cerebral oedema	42 %	37 %	39 %
Meningeal oedema	20 %	13 %	16 %

TABLE 2

Combinations of main causes of death found at autopsy in 122 patients dying in the neonatal period

	BW > 2500 gm 55 pat.	BW < 2500 gm 67 pat.	Total 122 pat
Pulmonary atelectasis Normal brain (20 patients)	9 %	22 %	16 %
Pulmonary atelectasis Cerebral oedema (19 patients)	16 %	15 %	15 %
Pulmonary atelectasis Cerebral haemorrh. ± oedema (61 patients)	49 %	51 %	50 %
Cerebral haemorrh. ± oedema Normal lungs (22 patients)	26 %	12 %	18 %

in the mature, while all other brain lesions—each only present in a few patients—were almost evenly distributed in the two groups.

Table 2 shows the combinations of causes of death. 16 per cent, or 20 patients, a majority of whom were premature, had no brain damage. Correspondingly there was a preponderance of mature infants in the 18 per cent, or 22 cases, which had only cerebral changes. However these groups are small. In the largest group (65 per cent) with both cerebral and pulmonary changes, the proportion of mature and premature patients was about equal.

Secondary findings

In one patient, who had severe intracranial haemorrhage, autopsy revealed a mild internal hydrocephalus and a unilateral double renal pelvis and ureter.

One patient as well as a tentorial tear had a thrombosis of the transverse sinus. Apart from these two cases no additional intracranial abnormalities were observed.

Moreover malformations were observed in only two patients. In one infant, who had an intracranial haemorrhage as well as cerebral oedema and atelectases, a horseshoe kidney was found. Another patient with a tentorial tear had a mild goitre and slight hyperplasia of the thymus.

Persistent ductus arteriosus and patent foramen ovale, which can hardly be considered malformations at that age, were frequent. They were found to be co-existent in 48 per cent of the cases. Persistent ductus arteriosus was found in a total of 56 per cent and patent foramen ovale in 53 per cent of the cases, with no appreciable difference between the weight groups.

No cases of hyaline membrane disease were disclosed, however, no histological studies of the lungs had been carried out.

Abnormal intrathoracic findings were as follows. One case of haematopneumothorax following rupture of the inferior lobe in the left lung; one of mild hydrothorax, seven cases of tracheo-bronchitis, one case of pneumonia, one patient had subendocardial haemorrhage and four had subpericardial haemorrhages. Two of the latter also had petecchial haemorrhages in the thymus, as had two further patients.

Abnormal intra-abdominal findings were: Two cases of intraperitoneal haemorrhage, one of unknown origin and one following rupture of the spleen, two cases of subcapsular haemorrhage of the kidney: three of subcapsular haemorrhage of the liver. Fourteen patients had varying degrees of suprarenal haemorrhage, one had parenchymatous liver degeneration and uric acid infarcts in the renal papillae.

Even though some of these conditions undoubtedly represent contributory causes of death, those listed in Table 2 were considered by the pathologists to be the primary causes.

2 Survivors of the neonatal period

The 153 patients surviving the neonatal period have been divided into four groups.

I 29 patients with severe cerebral sequelae

These patients, representing 11 per cent of the total series and 19 per cent of the survivors, are again divided into three groups.

1) 18 patients were mentally retarded and had severe neurological symptoms,
2) 7 patients were mentally retarded and had physical handicaps of varying degrees,
3) 4 patients were of normal intelligence, but had definite, though not disabling neurological symptoms

18 patients were boys, 11 were girls.

Table 3 lists the principal clinical findings. (For details see case reports nos. 1 to 29)

Heredity Family histories failed to reveal cerebral disease except in two cases (nos. 11 and 23) where there was a history of epilepsy in close relatives. Both these patients were mentally retarded and one had seizures.

The mortality was high in this group 12 patients out of 29 had died. All of these were mentally retarded, 11 also had quadriplegia, the twelfth exhibited no neurological features, but had a severe hydrocephalus. The commonest cause of death was infection of the respiratory tract. One patient had died from meningitis. The age at death ranged from 2 months to 4$^1/_2$ years, seven were from 2 to 3 years old, three died before their second year and two were well over 4 years old.

The mental development was seriously retarded in the great majority of the first two groups sixteen of the children were under the care of Statens Andssvageforsorg (S A.) (the National Service for the Mentally Retarded) Of the remaining nine, four had died at the age of 2 months, 6 months, 1$^1/_2$ years and 2 years, respectively (Nos. 3 10 17 and 1) It can be assumed that they would have been under the care of S A had they lived.

Of the last five, three with obvious mental defects were not, however under public care primarily owing to the refusal of their parents. The remaining two probably had a subnormal intelligence, but evaluation was difficult because of multiple handicaps (nos. 4 and 7)

TABLE 3

A survey of the principal clinical findings in 29 patients with severe cerebral sequelae

	No. pat.	Macro-cephaly	Hydro-cephaly	Convul-sions	Aphasia	Speech defect	Hypa-cusis	Squint	Nystag-mus	Dead	Under care (SA)*)
1 Mental deficiency plus a) quadriplegia	16	10	2	13	9	3	2	9	6	11	9
b) ataxia	2	–	–	–	2	–	1	1	–	–	1
2. Mental deficiency plus motor retardation, no neurol. symptoms	7	2	3	2	6	–	1	2	–	1	6
3 Normal intelligence plus a) athetosis	1	–	–	–		1	1	1	–	–	–
b) paraplegia	2	–	1	1	–	–	–	2	–	–	–
c) hemiplegia	1	–	–	–	–	–	–	–	–	–	–
Total	29	12	6	16	17	4	5	15	6	12	16

) *The National Servic for the Mentally Retarded*

2 Survivors of the neonatal period

The 153 patients surviving the neonatal period have been divided into four groups:

I 29 patients with severe cerebral sequelae

These patients, representing 11 per cent of the total series and 19 per cent of the survivors, are again divided into three groups

1) 18 patients were mentally retarded and had severe neurological symptoms,
2) 7 patients were mentally retarded and had physical handicaps of varying degrees,
3) 4 patients were of normal intelligence, but had definite, though not disabling neurological symptoms.

18 patients were boys, 11 were girls.

Table 3 lists the principal clinical findings (For details, see case reports nos 1 to 29)

Heredity Family histories failed to reveal cerebral disease except in two cases (nos. 11 and 23) where there was a history of epilepsy in close relatives. Both these patients were mentally retarded and one had seizures.

The mortality was high in this group 12 patients out of 29 had died. All of these were mentally retarded, 11 also had quadriplegia, the twelfth exhibited no neurological features, but had a severe hydrocephalus. The commonest cause of death was infection of the respiratory tract. One patient had died from meningitis The age at death ranged from 2 months to 4½ years, seven were from 2 to 3 years old, three died before their second year and two were well over 4 years old.

The mental development was seriously retarded in the great majority of the first two groups. sixteen of the children were under the care of Statens Andssvageforsorg (S. A.) (the National Service for the Mentally Retarded) Of the remaining nine, four had died at the age of 2 months, 6 months, 1½ years and 2 years, respectively (Nos. 3 10 17 and 1) It can be assumed that they would have been under the care of S. A had they lived.

Of the last five, three with obvious mental defects were not, however under public care, primarily owing to the refusal of their parents. The remaining two probably had a subnormal intelligence, but evaluation was difficult because of multiple handicaps (nos 4 and 7)

TABLE 4

EEG-findings in relation to the presence or absence of seizures in 29 patients with severe cerebral sequelae

	Abnormal EEG	Normal EEG	No EEG	Total
Convulsions	11	1	4	16
No convulsions	2	7	4	13
Total	13	8	8	29

measurement of the head circumference and description of brain sections.

Electroencephalograms were obtained in 21 of the 29 cases. Of these 13 were abnormal (Table 4)

EEG-abnormalities were observed in two patients who had never had seizures. One had a severe quadriplegia, and the EEG had been recorded at the age of one year (no. 9 dying when well over 4 years of age) The other patient, aged 13 years, had ataxia (no. 4) Her EEG dated back to the age of 6 years. 11 of the 16 children with seizures had EEG-abnormalities (four had had no EEGs taken) One of the children with seizures had a normal EEG (no. 14) her seizures, occurring at the age of 9–10 months, showed an atypical pattern, described as twitchings and jerks. Her EEG had been taken when she was one year old. This patient, who had a quadriplegia, had been seen for the last time at the age of four years.

An additional 7 children, whose EEGs were normal, had, at least up to the time of the follow-up, been seizurefree. Of these, two had quadriplegia (no. 7 EEG taken at 2 years, and no 8, EEG taken at 5 months) one patient had athetosis (no. 28, EEG at 5 years) and four were physically and

TABLE 5

EEG-findings in 29 patients with severe cerebral sequelae

	Number pat.	Abnormal EEG	Normal EEG	No EEG
1 Mental retardation with				
a) quadriplegia	16	9	3	4
b) ataxia	2	2	0	0
2. Mental retardation without neurological symptoms	7	1	4	2
3 Normal intelligence with				
a) athetosis	1	0	1	0
b) paraplegia	2	1	0	1
c) hemiplegia	1	0	0	1

The physical handicaps were serious in most of the mentally defective. 14 out of 16 patients with quadriplegia were severely spastic, one was moderately spastic, but also ataxic (no 2) one had a mild quadriplegia and, in addition, a severe hemiplegia following a violent convulsion at the age of 3 years (no. 6)

None of the twelve patients who had died had been able to walk. Three mentally retarded patients exhibiting neurological symptoms were unable to walk at the time of the follow-up (aged 4–14) two walked at 4 and 6 years, and two walked at around 3 years, all with difficulty Of the mentally defectives who failed to exhibit neurological features, four walked at 2 years, one at 3 and one at about 4 years.

Of the children with normal intelligence two walked at around the age of 2 and two at about 3 years.

Seizures occurred in more than half of the patients (16 out of 29) the greatest number among quadriplegics (13 of 16)

The commonest type of seizures were generalized clonic convulsions (13 patients) One patient had fainting spells (no 24) two patients had spells described as infantile spasms (pat. nos. 13 and 20)

Speech. 17 patients, all among the mentally retarded, exhibited severe speech defects and are listed in Table 3 as aphasic. (Seven of these, however had died before the age of 3 without ever having been able to speak) Four had moderate speech defects—three of these were mentally retarded, the fourth (no 28) whose intelligence was normal, had a mild athetosis and impaired hearing.

Four had normal speech, and, with the exception of one mentally defective, also normal intelligence.

On four patients, all dying within the first two years of life, there was no information about speech.

Hearing defects were found in at least five patients, who also had speech difficulties of varying degrees. One was the above mentioned athetotic child of normal intelligence The other four were mentally retarded. In two there was a complete lack of response to noise (nos. 15 and 18) the last two had a slight hearing loss. Both had been seen by an otologist.

Vision A squint was present in about half the patients. Impaired vision was thought to be a feature in six patients who had nystagmus (all of them quadriplegics) Four of these also had a squint.

Visual acuity was not measured at the follow-up examination however there was no evidence of impaired vision apart from the six cases above.

Special examinations

In a number of patients an objective evaluation of the cerebral state was obtained by electroencephalograms (EEG) pneumoencephalograms (PEG)

TABLE 4

EEG-findings in relation to the presence or absence of seizures in 29 patients with severe cerebral sequelae

	Abnormal EEG	Normal EEG	No EEG	Total
Convulsions	11	1	4	16
No convulsions	2	7	4	13
Total	13	8	8	29

measurement of the head circumference and description of brain sections.

Electroencephalograms were obtained in 21 of the 29 cases. Of these 13 were abnormal (Table 4)

EEG-abnormalities were observed in two patients who had never had seizures. One had a severe quadriplegia, and the EEG had been recorded at the age of one year (no 9 dying when well over 4 years of age) The other patient, aged 13 years, had ataxia (no. 4) Her EEG dated back to the age of 6 years. 11 of the 16 children with seizures had EEG-abnormalities (four had had no EEGs taken) One of the children with seizures had a normal EEG (no. 14) her seizures, occurring at the age of 9–10 months, showed an atypical pattern, described as twitchings and jerks. Her EEG had been taken when she was one year old. This patient, who had a quadriplegia, had been seen for the last time at the age of four years.

An additional 7 children, whose EEGs were normal, had, at least up to the time of the follow-up, been seizurefree. Of these, two had quadriplegia (no. 7 EEG taken at 2 years, and no 8, EEG taken at 5 months) one patient had athetosis (no. 28, EEG at 5 years) and four were physically and

TABLE 5

EEG-findings in 29 patients with severe cerebral sequelae

	Number pat.	Abnormal EEG	Normal EEG	No EEG
1. Mental retardation with				
a) quadriplegia	16	9	3	4
b) ataxia	2	2	0	0
2. Mental retardation without neurological symptoms	7	1	4	2
3 Normal intelligence with				
a) athetosis	1	0	1	0
b) paraplegia	2	1	0	1
c) hemiplegia	1	0	0	1
Total	29	13	8	8

mentally retarded, two being hydrocephalic, one microcephalic. (Nos 21 EEG at one year 22 EEG at 1 1/2 years 23 EEG at 1 1/2 years, and 25 EEG at 4 1/2 years)

The distribution of normal and abnormal findings within the diagnostic groups is seen in Table 5

The EEG abnormalities had no common features. Detailed descriptions are found in the case reports. In seven patients without focal neurological features there were focal EEG abnormalities, with spikes or spikes and spike-waves of diverse origins. Four had generalized abnormalities with multiple spikes and spike-waves One patient (no 15 with severe cerebral atrophy) had an atypical record with absence of activity in the central-parietal and central tracings as well as random spikes frontally and temporally One patient (no 13) had severe abnormalities with discharges of low frequency and high amplitude over the right hemisphere. The record had a focal character not suggestive of hypsarrhythmia. (This child had seizures resembling infantile spasms) The second patient who had attacks described as infantile spasms (no 20) had never had an EEG taken.

Head circumference was measured in 20 patients As will be seen from Fig. 2 the measurements were above normal in four below normal in nine, and within the normal range in seven patients An additional two patients have in Table 3 been classified as hydrocephalic: In one case (no 10) the exact figure was not stated, however the record mentioned an abnormally fast increase in the head circumference over a certain period of time, and the diagnosis had been substantiated by PEG The second patient (no 22) had a normal measurement, but PEG revealed a mild internal hydrocephalus.

Of 12 microcephalic patients in Table 3 only nine had been measured However two patients brains (nos 15 and 16) were found to be abnormally small on section and one patient s (no 12) record contained repeated notes describing the child as microcephalic.

As seen from Table 3 all the microcephalic patients were in the group of mentally defectives as were all but one of the hydrocephalics. This patient (no 27) had paraplegia and convulsions

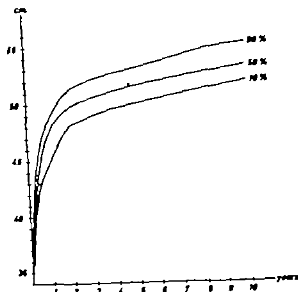
Pneumoencephalography had been performed in 13 of the 29 cases. All but one (no 28 with athetosis) were abnormal (case reports nos. 6 10 12, 13 15 16 17 18 20 21 22 and 27)

The diagnosis of hydrocephalus was confirmed in four patients and disclosed in one patient with normal head circumference. (no 22)

The cerebral atrophy that could be expected in the microcephalics was confirmed in the six cases where PEG studies had been made.

Cerebral atrophy was also demonstrated in one patient, whose head circumference had not been measured (no 6)

Boys



Girls

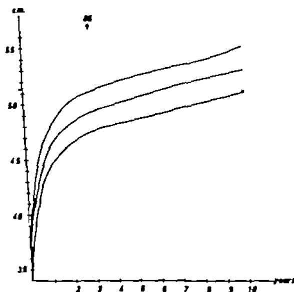


Fig. 2

Head circumference in centimetres, measured at follow-up, in 29 patients with severe cerebral sequelae. (Tracings from Vickers and Stuart, J. Pediat. 1943 22 155).

mentally retarded, two being hydrocephalic, one microcephalic. (Nos 21 EEG at one year 22, EEG at 1½ years 23 EEG at 1½ years, and 25 EEG at 4½ years)

The distribution of normal and abnormal findings within the diagnostic groups is seen in Table 5

The EEG-*abnormalities* had no common features. Detailed descriptions are found in the case reports In seven patients without focal neurological features there were focal EEG abnormalities, with spikes or spikes and spike waves of diverse origins. Four had generalized abnormalities with multiple spikes and spike-waves. One patient (no 15 with severe cerebral atrophy) had an atypical record with absence of activity in the central-parietal and central tracings as well as random spikes frontally and temporally One patient (no 13) had severe abnormalities with discharges of low frequency and high amplitude over the right hemisphere. The record had a focal character not suggestive of hypsarrhythmia. (This child had seizures resembling infantile spasms) The second patient who had attacks described as infantile spasms (no 20) had never had an EEG taken.

Head circumference was measured in 20 patients As will be seen from Fig. 2, the measurements were above normal in four below normal in nine, and within the normal range in seven patients. An additional two patients have in Table 3 been classified as hydrocephalic. In one case (no 10) the exact figure was not stated, however the record mentioned an abnormally fast increase in the head circumference over a certain period of time and the diagnosis had been substantiated by PEG The second patient (no 22) had a normal measurement, but PEG revealed a mild internal hydrocephalus

Of 12 microcephalic patients in Table 3 only nine had been measured However two patients brains (nos 15 and 16) were found to be abnormally small on section and one patient's (no 12) record contained repeated notes describing the child as microcephalic

As seen from Table 3 all the microcephalic patients were in the group of mentally defectives as were all but one of the hydrocephalics. This patient (no 27) had paraplegia and convulsions

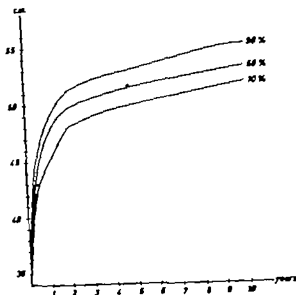
Pneumoencephalography had been performed in 13 of the 29 cases. All but one (no 28 with athetosis) were abnormal (case reports nos. 6 10 12 13 15 16 17 18 20, 21 22 and 27)

The diagnosis of hydrocephalus was confirmed in four patients and disclosed in one patient with normal head circumference. (no 22)

The cerebral atrophy that could be expected in the microcephalics was confirmed in the six cases where PEG-studies had been made.

Cerebral atrophy was *also demonstrated* in one patient, whose head circumference had not been measured (no 6)

Boys



Girls

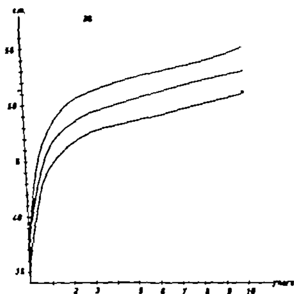


Fig. 2

Head circumference in centimetres, measured at follow-up, in 29 patients with severe cerebral sequelae. (Tracings from Vickers and Stuart, J. Pediat. 1943, 22, 155).

mentally retarded two being hydrocephalic, one microcephali EEG at one year 22 EEG at $1^1/_2$ years 23 EEG at $1^1/_2$ yea EEG at $4^1/_2$ years)

The distribution of normal and abnormal findings within the groups is seen in Table 5

The EEG-abnormalities had no common features. Detailed des are found in the case reports In seven patients without focal neur features there were focal EEG abnormalities, with spikes or spik spike-waves of diverse origins. Four had generalized abnormaliti multiple spikes and spike-waves. One patient (no 15 with severe cer atrophy) had an atypical record with absence of activity in the cen parietal and central tracings as well as random spikes frontally and t porally One patient (no 13) had severe abnormalities with discharges of l frequency and high amplitude over the right hemisphere. The record had focal character not suggestive of hypsarrhythmia. (This child had seizur resembling infantile spasms) The second patient who had attacks describ as infantile spasms (no. 20) had never had an EEG taken.

Head circumference was measured in 20 patients. As will be seen from Fig. 2, the measurements were above normal in four below normal in nine and within the normal range in seven patients. An additional two patients have in Table 3 been classified as hydrocephalic In one case (no 10) the exact figure was not stated, however the record mentioned an abnormally fast increase in the head circumference over a certain period of time, and the diagnosis had been substantiated by PEG The second patient (no 22) had a normal measurement, but PEG revealed a mild internal hydroce phalus.

Of 12 microcephalic patients in Table 3 only nine had been measured. However two patients brains (nos. 15 and 16) were found to be abnor mally small on section, and one patient's (no 12) record contained repeated notes describing the child as microcephalic.

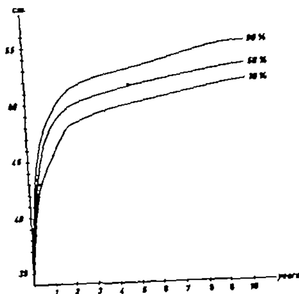
As seen from Table 3 all the microcephalic patients were in the group of mentally defectives, as were all but one of the hydrocephalics. This pa tient (no 27) had paraplegia and convulsions.

Pneumoencephalography had been performed in 13 of the 29 cases. All but one (no 28 with athetosis) were abnormal (case reports nos. 6 10 12 13 15 16 17 18 20 21 22 and 27)

The diagnosis of hydrocephalus was confirmed in four patients and dis closed in one patient with normal head circumference. (no 22)

The cerebral atrophy that could be expected in the microcephalics was confirmed in the six cases where PEG-studies had been made.

Cerebral atrophy was also demonstrated in one patient, whose head cir cumference had not been measured (no 6)



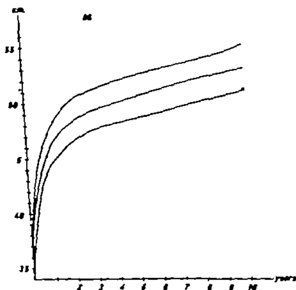


Fig. 2

Head circumference in centimetres, measured at follow-up, in 29 patients with severe cerebral sequelae. (Tracings from Vickers and Stuart, J. Pediat. 1943, 22 : 155).

Brain section. Detailed pathological reports were obtainable in 7 of the 12 deaths (case reports nos. 3 8 13 15 16 18 and 20)

All of these revealed severe pathological findings. Four had polyporencephaly and three had moderate hydrocephalus. One of these had dysgenesis of the corpus callosum, one had an Arnold-Chiari syndrome and in one there was a cerebral dysplasia with degeneration of the basal ganglia. No other malformations were disclosed

As seen from Table 6 cerebral atrophy has been demonstrated by PEG and/or brain section in a total of 14 cases. Six of the microcephalics and one hydrocephalic were not examined by either of these methods. However the clinical findings indicate the presence of cerebral atrophy in these cases also

Thus makes a total of 21 patients with cerebral atrophy out of 29 in this group

TABLE 6

Pneumoencephalography and brain section in relation to head circumference in 29 patients with severe cerebral sequelae

Head circumference	No. pat.	Abnormal PEG no brain sect.	Abnormal PEG plus brain sect.	Abnormal brain sect. no PEG	Normal PEG, no brain sect.	No PEG no brain section
Abnormally large	5	3	1	0	0	1
Abnormally small	12	2	4	0	0	6
Normal	7	1	0	1	1	4
Not measured	5	1	0	1	0	3
Total	29	7	5	2	1	14

Table 7 shows the distribution of the pathological findings within the diagnostic groups.

TABLE 7

Pneumoencephalography and brain section in 29 patients with severe cerebral sequelae

	No. pat.	Abnormal PEG, no brain sect.	Abnormal PEG plus brain sect.	Abnormal brain sect No PEG	Normal PEG no brain sect.	N PEG no brain section
1 Mental retardation with						
a) quadriplegia	16	4	4	2	-	6
b) ataxia	2	-	-	-	-	2
2. Mental retard. No neurological symptoms	7	2	1	-	-	4
3 Normal intellig. with						
a) athetosis	1	-	-	-	1	-
b) paraplegia	2	1	-	-	-	1
c) hemiplegia	1	-	-	-	-	1
Total	29	7	5	2	1	14

TABLE 8

Relationship between EEG and PEG and/or brain section in 29 patients with severe cerebral sequelae

	Abnormal PEG and or brain section	Normal PEG	No PEG	Total
Abnormal EEG	8	–	5	13
Normal EEG	3	1	4	8
No EEG	3	–	5	8
Total	14	1	14	29

Table 8 illustrates the correlation between EEG and PEG-findings. Three patients with confirmed brain atrophy had normal EEGs. In five cases, where no PEG was made, the clinical diagnosis of cerebral damage was substantiated by abnormal EEGs.

II Patients with minor cerebral sequelae

This group includes 24 children—9 per cent of the total material, or 16 per cent of the children who survived the neonatal period.

The group is heterogenous, with varying degree and type of handicap, all of which, however may be traced to the perinatal period. The majority of the patients had more than one symptom of cerebral damage.

A common feature of these patients is the absence of permanent motor handicap. The mental development had been normal except in a few cases, even these, however were only mildly retarded. There were no deaths in this group.

18 patients were boys and 6 were girls. The age at follow-up was from three to five years in 8, five to seven in 7 and over seven in 9 cases.

A description of each patient is given in the case reports nos. 30–53

The abnormal features are shown in *Table 9* and each will be dealt with in detail in the following sections.

The mental development was felt to be unsatisfactory in three patients. One of these (no. 41), on psychological testing at the age of 8, had an IQ of about 80, with allowance made for severe aphasia. Earlier testing had been abandoned due to the severe speech barrier. The second patient (no. 52) had an IQ score of 80 at the age of seven. He had begun school a few months earlier but had given up. He tried again the following year but had to be referred to a special class for backward children, where he did fairly well. No specific learning difficulties were observed.

The third patient (no. 30) had not been examined by a psychologist prior to follow-up, and testing was impractical for geographical reasons. Accord-

TABLE

A survey of abnormalities found in

Pat. no.	Mental retardation	Transient		Small size	Convulsions			D…
		Delayed developm.	Poor growth		Afebrile	Febrile	Breath holding	Hearing
30	(+)							
31					+			
32					+			
33					+			
34						+		
35		+	+		+			
36							+	
37			(+)					
38		+	+					
39								+
40								+
41	+	+	+					+
42								
43		+						
44								
45								
46								
47								
48								
49			+					
50								
51								
52	+			+				
53				+				
Total								
24	3	4	4	2	4	2	1	3

ing to her relatives she was, at the age of $6^1/_2$ somewhat backward, and she was also felt by the examiner to be rather dull.

The remaining 21 patients were in the opinion of the parents and also *of the examiner of normal intelligence. Four were also seen by a psychologist.*

Patient no 32 tested at the age of 12, had epileptic seizures and disturbed behaviour He had managed fairly well in normal classes at school though he had had to remain in the second form for an extra year He was de scribed by the psychologist as average or bright average, showing, however evidence of organic immaturity of the receptive aphasia-type. There were no speech difficulties.

One patient (no 36) who had retarded speech and behaviour disorder scored an IQ of 112 at the age of 6

Patient no 43 despite a pronounced lack of concentration and almost unintelligible speech, had an IQ score of 94 at the age of $2^1/_2$ In view of these handicaps his intelligence was considered to be even higher At the age

9
24 patients with minor cerebral sequelae

…fect			Strabismus				EEG		
Speech	Transient hypertonia	Behaviour disorder	Non-familial	Familial	Left handedness	Enuresis	Abn.	Norm.	None
			+			+	+		
			+				+		
		+				+	+		
			+		+			+	
								+	
			+		+			+	
+		+				+	+		
+		+	+					+	
+			+					+	
+								+	
+						+			+
+						+			+
+	+							+	
+		+							+
+									+
+									+
+								+	
+									+
+									+
+				+					+
+	+								+
+						+			+
						+			+
						+			+
16	2	4	6	1	2	8	4	8	12

of 6 his speech was essentially normal, but he was very restless. His development was considered compatible with his age.

Patient no. 46, who had an expressive and probably also mild receptive aphasia, obtained, at 6 years, an IQ of 101. His ability to concentrate was good, but Bender-Goldstein tests showed evidence of slight visuomotor defects suggesting organic brain damage.

Motor development was found to be transiently retarded in four patients, all of whom had exhibited inactivity and limpness throughout the first one or two years of life. They had not suffered noticeable intercurrent diseases. They were able to sit up respectively by 9, 12, 15 months and "late" and to walk by 15, 15, 20 and 22 months. Subsequently their motor pattern had been normal.

The two patients who walked by 15 months, even though this was not really late, are included in this group because, as already mentioned, they had been strikingly apathetic up to that time. Both had been born at term.

TABLE

A survey of abnormalities found in

Pat. no.	Mental retardation	Transient		Small size	Convulsions			De
		Delayed developm.	Poor growth		Afebrile	Febrile	Breath holding	Hearing
30	(+)							
31					+			
32					+			
33					+			
34						+		
35		+	+		+			
36							+	
37			(+)					
38		+	+					
39								+
40								+
41	+	+	+					+
42								
43		+						
44								
45								
46								
47								
48								
49			+					
50								
51								
52	+			+				
53				+				
Total 24	3	4	4	2	4	2	1	3

ing to her relatives she was at the age of 6½, somewhat backward, and she was also felt by the examiner to be rather dull

The remaining 21 patients were in the opinion of the parents and also of the examiner of normal intelligence. Four were also seen by a psychologist.

Patient no 32, tested at the age of 12, had epileptic seizures and disturbed behaviour He had managed fairly well in normal classes at school though he had had to remain in the second form for an extra year He was described by the psychologist as average or bright average, showing, however evidence of organic immaturity of the receptive aphasia-type. There were no speech difficulties.

One patient (no 36) who had retarded speech and behaviour disorder scored an IQ of 112 at the age of 6

Patient no 43 despite a pronounced lack of concentration and almost unintelligible speech, had an IQ score of 94 at the age of 2½ In view of these handicaps his intelligence was considered to be even higher At the age

37) it was unilateral and probably caused by recurrent middle ear infection. Hence this patient has not been included in this group.

In the other three (see Table 9) the hearing loss was bilateral and most pronounced for high frequencies. None of these patients had a history of otitis. All had been examined by otologists. Two had been provided with hearing-aids. All had speech difficulties in varying degree.

One patient (no. 39) had a family history of hearing loss, however the diagnosis at the National Centre for the Deaf was bilateral nerve deafness caused by premature birth. There was no family history in the remaining cases. In one (no. 40) the otologist at the Centre felt that the condition was caused by birth injury. In the second case no aetiology was suggested.

Two patients were seriously premature (BW below 1500 grams) the third was born at term.

Speech difficulties were found in varying degree in 16 patients, 12 boys and 4 girls examined at ages four to twelve years.

One patient (no. 48) who was only three years old at follow-up, has nevertheless been included, since at that time she was only able to utter a number of single words, which, though correctly pronounced, she could not combine into sentences.

The three patients with hearing loss had speech disorders in the form of imperfect formation of consonants. Two had received speech therapy at the age of six, but now spoke correctly when followed-up at the age of 12 and 11 years, respectively. The third child had "outgrown" his speech defect at the age of eight, without the aid of speech therapy.

The child who had a unilateral hearing loss (no. 37) following recurrent otitis had incorrect pronunciation until the age of six, after which his speech spontaneously became normal. The remaining children had normal hearing.

Two patients had received speech therapy at the age of seven and six respectively. They were found to have aphasia, chiefly of the expressive type. One (no. 41) was seriously handicapped. At the time of follow-up, aged 8½ years, his speech was very defective, and even as late as the age of sixteen he still had unmistakable speech trouble. The speech of the second child was characterized by defective articulation of consonants and occasional agrammatical errors. His later outcome is unknown (no. 46).

An additional patient (no. 36) had received speech therapy at the age of six because of speech defect. After a few months his speech became normal.

None of the remaining patients had received speech therapy. At follow-up, at ages 4 to 7 their speech had an immature character with occasional defective articulation of consonants. One of these children is known to have spoken normally by the age of 8½.

To sum up, considerable speech defects were found in two patients, who also had hearing loss. One patient had a severe aphasia and one had a

There were two cases of left handedness in this group

Growth Slow growth was seen in six patients In four it was only transient, in two more prolonged.

The first four children showed poor growth during the first 6 months to two years of life. Intercurrent disease was not reported within that period, and subsequent growth was normal Two of these children were born at term one had a BW of 2400 grams, the fourth weighed 1440 grams only but started normal growth earlier than any of the other three.

An additional patient had a history of poor growth during the first six years of life, coinciding with numerous infectious diseases At the time of follow-up when he was some 8 years old he had, however reached a height 6 cm above average and weighed almost 9 kg more than the average height/weight.

Two patients, despite normal birth weights, had always been considerably smaller than average. One, at 11½ years was 20 cm below average, the other showed a deficit of 10 cm at 4½ years. None had experienced noticeable intercurrent illnesses There were no instances of subnormal height in the families.

The remainder of this group had normal growth rates and their heights at the time of follow-up were largely within the normal range.

Convulsions were reported in six patients all had experienced more than one episode.

In three patients there were recurrent afebrile convulsions and their EEGs showed dysrhythmia indicative of epilepsy In one of these (no 31) the fits had ceased spontaneously at the age of three years. She had been seen last when she was six. The other two still had seizures at the age of six and twelve despite anti-convulsant therapy (nos 30 and 32)

Two of the children had convulsions in connection with fever Patient no 33 had suffered numerous attacks of increasing duration Patient no 34 had only one fit in connection with fever however he also had very frequent episodes of ill-defined absence-like type. Both had normal EEGs. None had received anti-convulsant drugs. They were four and three years old at the time of follow up

The sixth patient (no 35) had experienced two seizures at the age of two to four years, probably precipitated by temper tantrums. He, too had a normal EEG and had not received anti-convulsant therapy He had been seizure-free for well over three years at the time of follow-up

There was no family history of convulsion in any of the cases.

Two patients (nos. 30 and 32) thus had obvious epilepsy two (nos. 33 and 34) were highly suspicious of epilepsy and two (nos. 31 and 35) had a tendency towards seizures, from which they had apparently recovered.

Reduced hearing was found in a total of four patients. In one case (no

37) it was unilateral and probably caused by recurrent *middle ear infection*. Hence this patient has not been included in this group.

In the other three (see Table 9) the hearing loss was bilateral and most pronounced for high frequencies. None of these patients had a history of otitis. All had been examined by otologists. Two had been provided with hearing-aids. All had speech difficulties in varying degree.

One patient (no. 39) had a family history of hearing loss, however the diagnosis at the National Centre for the Deaf was bilateral nerve deafness caused by premature birth. There was no family history in the remaining cases. In one (no. 40) the otologist at the Centre felt that the condition was caused by birth injury. In the second case no aetiology was suggested.

Two patients were seriously premature (BW below *1500 grams*) *the third* was born at term.

Speech difficulties were found in varying degree in 16 patients, 12 boys and 4 girls examined at ages four to twelve years.

One patient (no. 48) who was only three years old at follow-up, has nevertheless been included, since at that time she was only able to utter a number of single words, which, though correctly pronounced, she could not combine into sentences.

The three patients with hearing loss had speech disorders in the form of imperfect formation of consonants. Two had received speech therapy at the age of six, but none spoke correctly when followed-up at the age of 12 and *11 years, respectively. The third child had "outgrown"* his speech defect at the age of eight, without the aid of speech therapy.

The child who had a unilateral hearing loss (no. 37) following recurrent otitis had incorrect pronounciation until the age of six, after which his speech spontaneously became normal. The remaining children had normal hearing.

Two patients had received speech therapy at the age of seven and six respectively. They were found to have aphasia, chiefly of the expressive type. One (no. 41) was seriously handicapped. At the time of follow-up, aged 8 $^{1}/_{2}$ years, his speech was very defective, and even as late as the age of sixteen he still had unmistakable speech trouble. The speech of the second child was characterized by defective articulation of consonants and occasional agrammatical errors. His later outcome is unknown (no. 46).

An additional patient (no. 36) had received speech therapy at the age of six because of speech defect. After a few months his speech became normal.

None of the remaining patients had received speech therapy. At follow-up, at ages 4 to 7 their speech had an immature character with occasional defective articulation of consonants. One of these children is known to have spoken normally by the age of 8$^{1}/_{2}$.

To sum up, considerable speech defects were found in two patients, who also had hearing loss. One patient had a severe aphasia and one had a

There were two cases of left handedness in this group

Growth Slow growth was seen in six patients in four it was only transient, in two more prolonged

The first four children showed poor growth during the first 6 months to two years of life. Intercurrent disease was not reported within that period, and subsequent growth was normal. Two of these children were born at term, one had a BW of 2400 grams, the fourth weighed 1440 grams only but started normal growth earlier than any of the other three.

An additional patient had a history of poor growth during the first six years of life, coinciding with numerous infectious diseases. At the time of follow up when he was some 8 years old, he had, however reached a height 6 cm above average and weighed almost 9 kg more than the average height/weight.

Two patients, despite normal birth weights, had always been considerably smaller than average. One, at 11$^1/_2$ years, was 20 cm below average the other showed a deficit of 10 cm at 4$^1/_2$ years. None had experienced notice able intercurrent illnesses. There were no instances of subnormal height in the families.

The remainder of this group had normal growth rates and their heights at the time of follow-up were largely within the normal range.

Convulsions were reported in six patients all had experienced more than one episode.

In three patients there were recurrent afebrile convulsions and their EEGs showed dysrhythmia indicative of epilepsy In one of these (no 31) the fits had ceased spontaneously at the age of three years. She had been seen last when she was six. The other two still had seizures at the age of six and twelve despite anti-convulsant therapy (nos. 30 and 32)

Two of the children had convulsions in connection with fever Patient no 33 had suffered numerous attacks of increasing duration. Patient no 34 had only one fit in connection with fever however he also had very frequent episodes of ill-defined absence-like type. Both had normal EEGs. None had received anti-convulsant drugs They were four and three years old at the time of follow-up

The sixth patient (no 35) had experienced two seizures at the age of two to four years, probably precipitated by temper tantrums. He, too had a nor mal EEG and had not received anti-convulsant therapy He had been seizure-free for well over three years at the time of follow-up

There was no family history of convulsion in any of the cases.

Two patients (nos. 30 and 32) thus had obvious epilepsy two (nos. 33 and 34) were highly suspicious of epilepsy and two (nos. 31 and 35) had a tendency towards seizures, from which they had apparently recovered.

Reduced hearing was found in a total of four patients. In one case (no

37) it was unilateral and probably caused by recurrent middle ear infection. Hence this patient has not been included in this group.

In the other three (see Table 9) the hearing loss was bilateral and most pronounced for high frequencies. None of these patients had a history of otitis. All had been examined by otologists. Two had been provided with hearing-aids. All had speech difficulties in varying degree.

One patient (no. 39) had a family history of hearing loss, however the diagnosis at the National Centre for the Deaf was bilateral nerve deafness caused by premature birth. There was no family history in the remaining cases. In one (no. 40) the otologist at the Centre felt that the condition was caused by birth injury. In the second case no aetiology was suggested.

Two patients were seriously premature (BW below 1500 grams) the third was born at term.

Speech difficulties were found in varying degree in 16 patients, 12 boys and 4 girls examined at ages four to twelve years.

One patient (no. 48) who was only three years old at follow-up, has nevertheless been included, since at that time she was only able to utter a number of single words, which, though correctly pronounced, she could not combine into sentences.

The three patients with hearing loss had speech disorders in the form of imperfect formation of consonants. Two had received speech therapy at the age of six, but none spoke correctly when followed-up at the age of 12 and 11 years, respectively. The third child had "outgrown" his speech defect at the age of eight, without the aid of speech therapy.

The child who had a unilateral hearing loss (no. 37) following recurrent otitis had incorrect pronounciation until the age of six, after which his speech spontaneously became normal. The remaining children had normal hearing.

Two patients had received speech therapy at the age of seven and six respectively. They were found to have aphasia, chiefly of the expressive type. One (no. 41) was seriously handicapped. At the time of follow-up, aged 8 $^1/_2$ years, his speech was very defective, and even as late as the age of sixteen he still had unmistakable speech trouble. The speech of the second child was characterized by defective articulation of consonants and occasional agrammatical errors. His later outcome is unknown (no. 46).

An additional patient (no. 36) had received speech therapy at the age of six because of speech defect. After a few months his speech became normal.

None of the remaining patients had received speech therapy. At follow-up, at ages 4 to 7 their speech had an immature character with occasional defective articulation of consonants. One of these children is known to have spoken normally by the age of $8^1/_2$.

To sum up, considerable speech defects were found in two patients, who also had hearing loss. One patient had a severe aphasia and one had a

presumably mild aphasia. The remaining twelve exhibited varying degrees of retarded speech development.

The behavioural pattern of 20 children appeared to be normal however two of these were described as being unusually hyperactive (patient no. 30 with epilepsy and no 46 with a mild aphasia) one as rather reserved and touchy (no 38 with hearing loss and speech defect) and one as vulnerable and quick tempered (no 41 with severe aphasia)

Four presented obvious behavioural deviations such as hyperactivity lack of concentration and aggression (nos. 32, 36 37 and 43) All of these had additional handicaps, and precipitating environmental factors have not been definitely excluded. Three were examined by a psychologist (see p. 38)

Transient hyperactivity in the form of screaming, restlessness and reduced need for sleep that could not be attributed to external factors, were present in two children (nos. 42 and 50) during the first one or two years of life. Of these one was also over sensitive to noise. Neither subsequently had presented any behavioural problems.

Eye defects Squint was present in seven patients (see Table 9) One also had diminished visual acuity in both eyes (no 35) another in one eye (no 37) The other patients vision was normal. Only one had a family history of squint (no 49) one child (no 32) had a unilateral presumably familial cataract.

Retrolental fibrosis was not observed.

Enuresis Eight patients had been, or were still, suffering from enuresis. In only one case (no 51) was there a family history of enuresis.

Behavioural defects in varying degree were present in four (nos. 30 32, 36 and 41) All eight children had various additional handicaps.

Electroencephalography had been performed in 12 cases (see Table 9) The records were abnormal in four patients, three of whom had a history of seizures. The fourth, at the age of 12 had never had seizures (no. 36) For full details reference may be made to the case histories

In the three patients who had experienced seizures the EEG showed abnormalities of varying severity with spikes of differing location indicative of epilepsy The record of the fourth patient, who presented a behavioural defect, revealed generalized dysrhythmia.

The eight normal EEGs were recorded as follows. two patients with febrile convulsions one with breathholding spells one with aberrant behaviour and speech disorder two with reduced hearing and speech defect, and two with speech disorders, one of these being aphasic.

III Patients with mild deviations of presumably cerebral origin

In this group are included 30 patients, or 11 per cent of the total material (19 per cent of the survivors)

Like Group II it is quite heterogeneous. Some symptoms are present in each group. The reason for nevertheless including the patients in this "milder" group is the fact that their symptoms were less pronounced and, in contrast to Group II usually occurred singly

In addition some of the patients had presented symptoms only transiently and were found to be normal at the time of follow-up.

Motor handicaps had not been demonstrated, and the mental deviations had been of a less definite kind than in the previous group

Eighteen children were boys, twelve were girls. 12 children were aged three to five, 9 were five to seven, and 9 were more than seven years old.

The symptoms are listed in Table 10. For a description of individual cases reference should be made to case reports nos. 54 to 83

The following sections contain an analysis of each symptom.

The mental development of these children was felt by the examiner as well as by the parents to be within normal limits in all cases. However, the evaluation is not entirely comprehensive, as no psychological tests had been performed and, in addition, many of the children were very young at the time of follow-up. Of the nine children attending school five had reading difficulties and achieved only medium marks at school, and one had had to remain a second year in the first form. These children's intelligence was felt to be within the normal range (cf. p. 46).

Motor development had been temporarily retarded in ten patients, six of whom also transiently showed poor growth. Until normal development started, lethargy had been marked, half the children were said to have been very flaccid.

The majority of the patients were able to sit up at the age of 9 to 10 months, although one not until the age of 18 months. Four walked at 14 to 15 months and the remainder at 18 months to 2 years. Of the first four one was premature, having a BW of 2400 grams, the remainder were full-term. Of the remaining six 4 were premature, with a BW of 1800–2000 grams. Their motor pattern had not been unusual except in the case of two patients. One (no. 64) was suspected of having cerebral palsy when admitted to hospital at the age of 4 months because of increased muscle tone and exaggerated tendon reflexes. She had evident rickets at that time. Follow-up examination revealed no spasticity. The second patient (no. 60) aged 10 years at follow-up, had always been slow at walking and running, characterized by rather pronounced flat feet. Although this had not altered over

TABLE

A survey of the findings in 30 patients

No. pat.	Transitory retarded development	Transitory poor growth	Small height	Convulsions	
				Febrile	Breath holding
54				+	
55				+	
56			+		+
57	+	+	+	+	
58	+				
59	+	+			
60	+				
61	+				
62	+	+			
63	+				
64	+	+			
65	+	+			
66	+	+			
67					
68					
69					
70					
71					
72					
73					
74					
75					
76					
77					
78					
79					
80					
81					
82					
83					
Total 30	10	6	2	3	1

the years, his motor pattern was otherwise normal. Hand movements were normal, and neurological examination was negative.

The remaining patients had developed normally sitting up at about 6 months and walking at about one year

There was one case of left-handedness (familial)

Growth. Transient retardation of growth was reported in six patients (cf Table 10) In three it persisted until the third to eighth month, and in the other three for the first two years of life. Growth later became normal except in one case where the height at the age of $7^1/_2$ years was found to be

10
with mild, presumably cerebral deviations

Transitory hyperactivity	Behaviour disorder	Dyslexia	Left-handedness	Squint: Non-paralytic	Squint: Paralytic	Enuresis	Abnorm. EEG
	+					+	
					+		+
				+			
		+					
		+					
+							
	+	+					
							+
+							
+							
+							
+							
+							
	+				+		+
	+				+		+
	+						+
		+	+	+		+	
						+	
						+	
						+	
					+	+	
		+					
							+
				+			
					+		
6	5	5	1	3	5	6	6

10 cm below average. This patient (no. 57) had a family history of small size. In addition he had stethoscopic evidence of heart disease, presumably a ventricular septal defect, which, however was symptomless.

One of the three patients who had exhibited poor growth for the first two years of life (no. 64) had, during the first year been thought to suffer from gluten intolerance and had been put on a temporary gluten-free diet without success. Another patient (no. 66) had rejected food over a prolonged period. Apart from these none had suffered from intercurrent illnesses.

Three of the patients were born at term, three were premature, the lowest

TABLE

A survey of the findings in 30 patients

No. pat.	Transitory retarded development	Transitory poor growth	Small height	Convulsions	
				Febrile	Breath holding
54					
55				+	
56			+	+	
57	+	+	+		+
58	+			+	
59	+	+			
60	+				
61	+				
62	+	+			
63	+				
64	+	+			
65	+	+			
66	+	+			
67					
68					
69					
70					
71					
72					
73					
74					
75					
76					
77					
78					
79					
80					
81					
82					
83					
Total 30	10	6	2	3	1

the years, his motor pattern was otherwise normal. Hand movements were normal, and neurological examination was negative.

The remaining patients had developed normally sitting up at about 6 months and walking at about one year

There was one case of left-handedness (familial)

Growth. Transient retardation of growth was reported in six patients (cf. Table 10) In three it persisted until the third to eighth month, and in the other three for the first two years of life. Growth later became normal except in one case where the height at the age of 7½ years was found to be

school. In one case (no. 75) there was also left-handedness, which—like the dyslexia—was familial. One additional patient only (no 80) had a family history of dyslexia.

Of the remaining children in this group 21 had not reached school age; three had just begun school, so that no evaluation was possible at the time. The last patient in the group, who was 13 years old, had no reading difficulties.

Speech development had been normal in all the children. One had a stammer however at the time of follow-up, at the age of $7^1/_2$ years, it was negligible. He had been receiving speech therapy for several years.

No *hearing defects* were observed.

Eye symptoms: Squint was present in eight patients, five of whom had a family history of this defect. Two (nos. 72 and 82) had diminished visual acuity in one eye. The vision of the remaining children was considered normal, and no other eye abnormalities were noted.

Enuresis was present in six patients, aged $4^1/_2$ to 10 years. One patient only (no. 77) had a family history of enuresis.

None of the six children had behaviour disorders two (nos. 76 and 77) were described as very sensitive. One further patient had dyslexia and a squint, and one had a (familial) squint.

Additional abnormalities: One patient (no. 57) had stethoscopic evidence of heart disease giving rise to no symptoms other than, possibly small height, which however was familial.

One patient (no. 64) at the age of $3^1/_2$ years had a very small head circumference (48 cm) Her development had been retarded during the first two years of life, but was subsequently normal. Head circumference of the other patients was normal.

Patient no. 81 had a left-sided ptosis as the only neurological feature present at follow-up. She had been delivered by forceps.

Electroencephalograms were normal in all six cases in which EEG-studies had been performed.

IV Patients with no abnormal features

70 children—40 boys and 30 girls—showed no abnormal features, i. e. 25 per cent of the total material and 46 per cent of the survivors. At follow-up 28 were aged three to five years, 23 were five to seven years, and 19 were more than seven years old.

Their mental development was estimated as normal on the basis of clinical observation and history. Those children who had already reached school age had started at the normal time and had done well. None had revealed difficulties of learning.

BW being 1800 grams. (This patient exhibited poor growth during the first four months only)

At the time of follow-up all except two had reached normal height: the one mentioned above, and patient no 56 whose height at $4^1/_2$ years was 8 cm below average. There was no history of periods with specifically poor growth or intercurrent disease. She was a twin, her BW being 1800 grams (the co-twin died when two days old) There was no family history of small size.

Convulsions occurred in four patients three had a single episode only of generalized clonic convulsions in connection with hyperpyrexia at the age of 4 2 and 1 year respectively The observation period following these episodes was 1 2 and 6 years, respectively and was thus too short for a prognostic evaluation in the first two cases.

The fourth patient had suffered repeated episodes of convulsions until 18 months of age, precipitated by crying. At the time of follow up, three years later there had been no further seizures.

None of the four patients had a family history of convulsions.

Behaviour disorders Six patients had exhibited transient hyperactivity in the form of crying, motor restlessness, occurring also when asleep, and often associated with a diminished need for sleep No environmental cause was apparent, and the symptoms subsided during the second year of life. These children presented no behaviour problems later on.

Five patients aged 4 to 10 years were reported to have behaviour disorders in the form of hyperactivity and violent temper The mothers denied precipitating environmental factors. One of these children had had febrile con vulsions, another was dyslectic and had temporarily shown retarded motor development. One had a (familial) squint and a marked sensitivity to noise. The fourth also had a (familial) squint. The fifth was otherwise normal.

Two patients (nos. 76 and 77) showed no obvious behavioural deviations, but were reported to be of "nervous temperament" and easily frightened One was a stammerer Environmental causative factors were also denied in these cases

An additional patient (no 66) appeared rather restless however the pa rents ascribed this to sibling jealousy" None of the remainder had presented behaviour disorders.

Dyslexia was present in five patients, all boys, aged 9 to 12 years at the time of follow-up

One of these children had been referred to the Institute for Dyslectics at the age of 12 following several years reading difficulties one had had to repeat the first form two had had to attend special classes in normal schools one had attended normal schools through his education. All were felt to have normal intelligence, though they obtained only medium marks at

school. In one case (no. 75) there was also *left-handedness*, which—like the dyslexia—was familial. One additional patient only (no. 80) had a family history of dyslexia.

Of the remaining children in this group 21 had not reached school age three had just begun school, so that no evaluation was possible at the time. The last patient in the group, who was 13 years old, had no reading difficulties.

Speech development had been normal in all the children. One had a stammer however, at the time of follow-up at the age of $7^1/_2$ years, it was negligible. He had been receiving speech therapy for several years.

No *hearing defects* were observed.

Eye symptoms: Squint was present in eight patients, five of whom had a family history of this defect. Two (nos. 72 and 82) had diminished visual acuity in one eye. The vision of the *remaining* children was considered normal, and no other eye abnormalities were noted.

Enuresis was present in six patients, aged $4^1/_2$ to 10 years. One patient only (no. 77) had a family history of enuresis.

None of the six children had behaviour disorders two (nos. 76 and 77) were described as very sensitive. One further patient had dyslexia and a squint, and one had a (familial) squint.

Additional abnormalities One patient (no. 57) had stethoscopic evidence of heart disease giving rise to no symptoms other than, possibly small height, which however was familial.

One patient (no. 64) at the age of $3^1/_2$ years had a very small head circumference (48 cm). Her development had been retarded during the first two years of life, but was subsequently normal. Head circumference of the other patients was normal.

Patient no. 81 had a left-sided ptosis as the only neurological feature present at follow-up. She had been delivered by forceps.

Electroencephalograms were normal in all six cases in which EEG-studies had been performed.

IV Patients with no abnormal features

70 children—40 boys and 30 girls—showed no abnormal features, i. e. 25 per cent of the total material and 46 per cent of the survivors. At follow-up 28 were aged three to five years, 23 were five to seven years, and 19 were more than seven years old.

Their mental development was estimated as normal on the basis of clinical observation and history Those children who had already reached school age had started at the normal time and had done well. None had revealed difficulties of learning.

BW being 1800 grams. (This patient exhibited poor growth during the first four months only)

At the time of follow-up all except two had reached normal height: the one mentioned above, and patient no 56 whose height at $4^{1}/_{2}$ years was 8 cm below average. There was no history of periods with specifically poor growth or intercurrent disease. She was a twin, her BW being 1800 grams (the co-twin died when two days old) There was no family history of small size.

Convulsions occurred in four patients three had a single episode only of generalized clonic convulsions in connection with hyperpyrexia at the age of 4 2 and 1 year respectively The observation period following these episodes, was 1 2 and 6 years respectively and was thus too short for a prognostic evaluation in the first two cases

The fourth patient had suffered repeated episodes of convulsions until *18 months of age, precipitated by crying. At the time of follow up three* years later there had been no further seizures.

None of the four patients had a family history of convulsions.

Behaviour disorders Six patients had exhibited transient hyperactivity in the form of crying, motor restlessness, occurring also when asleep, and often associated with a diminished need for sleep. No environmental cause was apparent, and the symptoms subsided during the second year of life. These children presented no behaviour problems later on.

Five patients aged 4 to 10 years were reported to have behaviour disorders in the form of hyperactivity and violent temper The mothers denied precipitating environmental factors. One of these children had had febrile convulsions, another was dyslectic and had temporarily shown retarded motor development. One had a (famililal) squint and a marked sensitivity to noise. The fourth also had a (familial) squint. The fifth was otherwise normal

Two patients (nos 76 and 77) showed no obvious behavioural deviations, but were reported to be of "nervous temperament" and easily frightened. One was a stammerer Environmental causative factors were also denied in these cases

An additional patient (no 66) appeared rather restless however the parents ascribed this to "sibling jealousy" None of the remainder had presented behaviour disorders.

Dyslexia was present in five patients, all boys, aged 9 to 12 years at the time of follow-up

One of these children had been referred to the Institute for Dyslectics at the age of 12 following several years reading difficulties one had had to repeat the first form two had had to attend special classes in normal schools one had attended normal schools through his education All were felt to have normal intelligence, though they obtained only medium marks at

of mixed type. *Barclay* (1956) found as many as 70 per cent out of 144 children with c. p. *Skatvedt* (1958) reported a percentage of 47 in a series of 370 patients with c. p. Finally *Eastman et al.* (1962) demonstrated neonatal abnormalities in 24 per cent of 689 cases of c. p. compared with only one per cent in a comparable series of controls. *Robson* (1962) found neonatal disease, including primary asphyxia, in 40 per cent of 198 children with c. p.

In the present material the incidence of c. p. is very high, 14 per cent compared with about 1.5/1000 in a normal population.

2. *Mental deficiency*

Similar studies, though less extensive, have been made on severe mental deficiency. *Larsen* (1931) in a series of 223 patients with mental retardation of exogenic origin, concluded that birth trauma was the most probable causative factor in 22 per cent of the cases.

Pasamanick and *Lilienfeld* (1955) found, in a survey of mentally retarded children, that 18 per cent had exhibited complications in the neonatal period compared with 7.5 per cent in a control material.

At postmortem examination *Benda* (1956) demonstrated abnormal findings of paranatal origin in 24 per cent of 258 mentally defective patients.

Drillien, Jameson and *Wilkinson* (1966) analysed a large series of mentally defectives (IQ below 70) for a variety of factors, including aetiology. In 13 per cent of 211 patients with an IQ below 55 and in 11 per cent with scores between 55 and 69 perinatal disorders were considered the most important aetiological factor. All these children had displayed varying symptoms during the neonatal period.

3. *Seizures*

The overall percentage of seizures in the present series is 18. If single episodes are disregarded, the percentage is 14.—Among the 29 patients with persisting neurological features the incidence, as already mentioned, was over 50 per cent and highest in quadriplegics (13 out of 16). Among the 124 patients with no neuro-muscular manifestations the incidence was 9 per cent; after omitting single episodes, 5 per cent. These figures include the febrile convulsions occurring in 4 per cent of the 124 cases.

The incidence of seizures in childhood is difficult to establish with certainty as not all children who have seizures are admitted to hospital and registration thus is incomplete. *Thom* (1941–42) gave a figure of 7 per cent among 3461 children under the care of the Community Health Association in Boston. *Bridge* (1949) found the same percentage among children admitted to Johns Hopkins Hospital over a three-year period. *Pache* (1954)

Their growth had been normal, and their height and weight as well as head circumference were within normal limits

Motor development had been normal in all cases, though 10 had not sat up until the age of 9–10 months and had not walked until the age of 12–18 months. At no time had there been a history of flaccidity or apathy

There were five cases of left handedness, of which two were familial.

Convulsions did not occur

All children had acquired toilet habits at the usual time.

There were no appreciable behaviour difficulties.

An EEG which was normal, had been recorded in only one patient, owing to nightmare like" nocturnal spells.

Discussion

All the features described above are presumably of cerebral origin. Whether or not they are sequelae of the neonatal condition will be discussed in detail in the following section.

1 *Cerebral palsy*

So far as Group I (severe handicaps) is concerned the relationship can hardly be questioned. Ever since Little s days there has been widespread agreement that patients suffering from cerebral palsy (c. p.)—whatever the origin—have frequently had neonatal disorders. Among recent studies (all retrospective) that of *Asher* and *Schonell* (1950) reported 221 cases of congenital c. p. in full-term children 38 per cent of whom had exhibited various symptoms during the neonatal period. *Belnap et al.* (1950) found that about half their series of 419 patients with c. p. had suffered birth in jury and a large majority of these had exhibited neonatal symptoms. *Lilienfeld* and *Parkhurst* (1951) found in 561 children with c. p a significantly higher incidence of complications during pregnancy delivery and neonatal period than in a comparable control series. They felt that there existed "a continuum of reproductive casualties" extending from foetal death to decreasing degrees of brain damage manifesting in neuropsychiatric disturbances. *Eastman and De Leon (1955)* reported "poor neonatal condition" in 42 per cent of 96 patients with c. p *Plum* in a study of c. p (1956) reported the presence of neonatal symptoms in 22 per cent of 87 hemiplegics, in 41 per cent of 91 paraplegics, in 66 per cent of 202 quadriplegics, and in about 60 per cent of 92 athetotics. *Crothers* and *Paine* (1959) made similar observations. neonatal symptoms were recorded in 28 per cent of 124 hemiplegics, in 36 per cent of 86 quadriplegics, in 47 per cent of 61 patients with extrapyramidal conditions and in 33 per cent of 57 patients with c. p

of mixed type. *Barclay* (1956) found as many as 70 per cent out of 144 children with c. p. *Skatvedt* (1958) reported a percentage of 47 in a series of 370 patients with c. p. Finally *Eastman et al.* (1962) demonstrated neonatal abnormalities in 24 per cent of 689 cases of c. p. compared with only one per cent in a comparable series of controls. *Roboz* (1962) found neonatal disease, including primary asphyxia, in 40 per cent of 198 children with c. p.

In the present material the incidence of c. p. is very high: 14 per cent compared with about 1.5/1000 in a normal population.

2. *Mental deficiency*

Similar studies, though less extensive, have been made on severe mental deficiency. *Larsen* (1931) in a series of 223 patients with mental retardation of exogenic origin, concluded that birth trauma was the most probable causative factor in 22 per cent of the cases.

Pasamanick and *Lilienfeld* (1955) found, in a survey of mentally retarded children, that 18 per cent had exhibited complications in the neonatal period compared with 7.5 per cent in a control material.

At postmortem examination *Benda* (1956) demonstrated abnormal findings of paranatal origin in 24 per cent of 258 mentally defective patients.

Drillien, Jameson and *Wilkinson* (1966) analysed a large series of mentally defectives (IQ below 70) for a variety of factors, including aetiology. In 13 per cent of 211 patients with an IQ below 55 and in 11 per cent with scores between 55 and 69 perinatal disorders were considered the most important aetiological factor. All these children had displayed varying symptoms during the neonatal period.

3. *Seizures*

The overall percentage of seizures in the present series is 18. If single episodes are disregarded, the percentage is 14.—Among the 29 patients with persisting neurological features the incidence, as already mentioned, was over 50 per cent and highest in quadriplegics (13 out of 16). Among the 124 patients with no neuro-muscular manifestations the incidence was 9 per cent, after omitting single episodes, 5 per cent. These figures include the febrile convulsions occurring in 4 per cent of the 124 cases.

The incidence of seizures in childhood is difficult to establish with certainty as not all children who have seizures are admitted to hospital and registration thus is incomplete. *Thom* (1941–42) gave a figure of 7 per cent among 3461 children under the care of the Community Health Association in Boston. *Bridge* (1949) found the same percentage among children admitted to Johns Hopkins Hospital over a three-year period. *Pache* (1954)

found as few as 3 7 per cent among the children admitted to the University Clinic of Paediatrics at Munich over a nine year period.

The incidence of febrile convulsions reported below is subject to the same reservations governing seizures in general However as in the latter case, they are fairly consistent. *Bridge* (1949) attributed 2 per cent of the admissions to Johns Hopkins Hospital over a three-year period to "febrile convulsions" *Bamberger* and *Matthes* (1959) in another hospital series, found 1 9 per cent. Among all children born in Heidelberg over a period of several years the percentage was 0 5–1 5 up to the fourth year of life. *Friderichsen* and *Melchior* (1954) in a hospital series over a four year period reported a percentage of 4 5

It is well known that seizures are a common feature in children with cerebral damage. The incidence of seizures in children with c. p has been assessed in several studies Thus *Perlstein* (1952) found this symptom in 40 per cent, occurring more often in spastics (50 per cent) than in athetotics (15 per cent) *Plum* (1956) found a frequency of 46 per cent in quadriplegics, 43 per cent in ataxics, 21–24 per cent in athetotics and 13 per cent in paraplegics.

The rates found in the present material are very similar although slightly higher than those given in non-selected series.

The aetiology of seizures is often obscure, though several workers have demonstrated a relation to birth injury

Livingston (1954) in a survey of 4158 epileptic children, found a history of head injury in 46 per cent. However in only 36 per cent was it felt to be severe enough to be considered the causative factor In 15 per cent of his large material the aetiology was thought to be birth injury In Livingston's opinion it is not possible, due to the difficulty of the neonatal diagnosis, to predict the frequency of later epilepsy in infants suffering birth injury

Peterman (1946) found a history of birth trauma in 14.2 per cent of a large series of epileptic children.

Bridge (1949) thought that natal or neonatal damage was an aetiological factor in 23 per cent of 742 epileptic children.

Nielsen and *Courville* (1951) felt that birth injury would seldom be the only causative factor in epilepsy except where there was a hereditary predisposition.

In a series of 535 epileptics, children as well as adults, gathered together by *Smith Robinson* and *Lennox* (1954) birth injury was found in 30 per cent and a prenatal aetiology was traced in 13 per cent of the cases.

Pasamanick and *Lilienfeld* (1955) studied the birth histories of 564 epileptic children and found the incidence of abnormalities during pregnancy delivery and the neonatal period to be significantly higher than in a comparable control material. The figures were identical whether the children had

a family history of epilepsy or not. However they found a significantly higher number of abnormalities in children whose seizures began within the first year of life.

In a series of 270 epileptic children *Bamberger* and *Matthes* (1959) found very high rates. They concluded that in 30 per cent the seizures could be ascribed to birth injury in 16 per cent to prenatal malformations, and in 8 per cent to either one or the other. *Peiffer*'s figures (1962–63) were considerably lower he ascribed 8.7 per cent to birth injury and 7 7 per cent to foetal abnormalities, as demonstrated by *pathological* studies in 298 epileptic patients.

Among workers considering birth injury to be a possible aetiological factor in febrile convulsions *Peterman* (1952) found an incidence of 11 per cent in a series of 302 patients. *Bamberber* and *Matthes* (1959) found a rate of 6.8 per cent birth injuries in 634 patients, and stated the frequency of birth trauma in just over 2000 births at the same time to be lower than 2 per cent. *Horstmann* and *Schlmmerling* (1963) disclosed a history of head injury in 17 per cent of 108 children with febrile convulsions, among which birth injury was by far the commonest.

It is evident that the connection between neonatal disorders and seizures cannot be proved. However, it may be said to exist with reasonable certainty

4 *Behaviour disorders*

It is an extremely difficult task to establish the reasons for deviation from what is recognized as normal behaviour. However a definite behavioural pattern seems strikingly common in children who have sustained brain damage in early life—even in the absence of neurological manifestations. This pattern is characterized by pronounced lack of concentration, hyperactivity aggression, emotional instability and immaturity It has been described with increasing frequency during the last 20 years (see among others *Bender* 1945 *Preston* 1945 *Rosenfeld* and *Bradley* 1948, *Bakwin* 1949 *Rogers* and *Lilienfeld* 1955 *Ingram* 1956, *Laufer* and *Denhoff* 1957 *Silver* 1958, *Lempp* 1964 and, for an extensive review of the literature *H H Nielsen* 1966)

The incidence of behaviour disorders (b. d.) due to brain damage is difficult to establish it varies considerably in reports from clinics concerned with the care of these children. The diagnosis has been made more frequently in recent years, as interest has increased and the diagnosis has been facilitated by the demonstration of the frequent co-existence of perceptual disorders.

EEG has been used in the diagnosis. *Jasper et al.* (1938) in 71 patients with b. d. found abnormal records in about three-quarters of the children with

found as few as 3 7 per cent among the children admitted to the University Clinic of Paediatrics at Munich over a nine-year period

The incidence of febrile convulsions reported below is subject to the same reservations governing seizures in general. However as in the latter case, they are fairly consistent. *Bridge* (1949) attributed 2 per cent of the admissions to Johns Hopkins Hospital over a three-year period to "febrile convulsions" *Bamberger* and *Matthes* (1959) in another hospital series, found 1 9 per cent. Among all children born in Heidelberg over a period of several years the percentage was 0.5–1 5 up to the fourth year of life. *Friderichsen* and *Melchior* (1954) in a hospital series over a four year period reported a percentage of 4 5

It is well known that seizures are a common feature in children with cerebral damage. The incidence of seizures in children with c. p has been assessed in several studies. Thus *Perlstein* (1952) found this symptom in 40 per cent, occurring more often in spastics (50 per cent) than in athetotics (15 per cent) *Plum* (1956) found a frequency of 46 per cent in quadriplegics, 43 per cent in ataxics, 21–24 per cent in athetotics, and 13 per cent in paraplegics.

The rates found in the present material are very similar although slightly higher than those given in non-selected series.

The aetiology of seizures is often obscure, though several workers have demonstrated a relation to birth injury

Livingston (1954) in a survey of 4158 epileptic children, found a history of head injury in 46 per cent. However in only 36 per cent was it felt to be severe enough to be considered the causative factor In 15 per cent of his large material the aetiology was thought to be birth injury In Livingston's opinion it is not possible, due to the difficulty of the neonatal diagnosis, to predict the frequency of later epilepsy in infants suffering birth injury

Peterman (1946) found a history of birth trauma in 14 2 per cent of a large series of epileptic children.

Bridge (1949) thought that natal or neonatal damage was an aetiological factor in 23 per cent of 742 epileptic children.

Nielsen and *Courville* (1951) felt that birth injury would seldom be the only causative factor in epilepsy except where there was a hereditary predisposition.

In a series of 535 epileptics, children as well as adults, gathered together by *Smith Robinson* and *Lennox* (1954) birth injury was found in 30 per cent and a prenatal aetiology was traced in 13 per cent of the cases.

Pasamanick and *Lilienfeld* (1955) studied the birth histories of 564 epileptic children and found the incidence of abnormalities during pregnancy delivery and the neonatal period to be significantly higher than in a comparable control material. The figures were identical whether the children had

neonatorum, *neonatal anoxia* and birth trauma, hereditary disorders and sequelae of maternal rubella) They found similarities in the audiograms of children with hearing loss due to morbus haemolyticus neonatorum and to anoxia, both groups showing a preponderance of selective hearing loss for high frequencies. This finding was substantiated by *Fisch* (1955), who found these similarities in the audiograms, though not consistent, but with suggestive frequency *Johnson* (1954) found, in 111 children with perceptual deafness, that in 10 per cent of the cases where no hereditary factors were demonstrable, the aetiology was perinatal asphyxia in another 10 per cent it was premature birth, without asphyxia. In these groups he found a well-defined hearing loss for high frequencies. His findings were supported by *Maran* (1966). *Flottorp Morley* and *Skarvedt* (1957) carried out audiological examinations in 10 athetoses (children and adolescents) which revealed a specific hearing loss for high frequencies. This was ascribed, however to cochlear defects.

Asrup (1959) examined ten pairs of twins, of whom one twin had a typical selective hearing loss for high frequencies, while the co-twin had normal hearing. Six of the ten pairs were premature. He found that loss of hearing was more likely to occur in a premature twin, if the BW was considerably lower than that of the co-twin, or if birth complications which predisposed to anoxia, such as breech presentation, were present, particularly in a first-born twin. However perinatal anoxia also led to partial hearing loss in full-term infants.

McDonald (1964) demonstrated moderate to severe hearing loss in 1 8 per cent of 1081 children with a BW below 1800 grams, when followed-up at the age of 6 to 8 years. The rate increased with decreasing gestational age (4 per cent in children born before the 33rd week and 0 6 per cent in children born after the 33rd week) Moreover the incidence was significantly higher (10.7 per cent) in children who had exhibited cyanotic attacks during the neonatal period than in those who had not (3 per cent) (In both groups the gestational age was below 33 weeks) He concluded that anoxia during the early postnatal period could result in impaired hearing in the very premature. This contrasts with the observations of *Davey* (1962) made on a much smaller series of premature children examined at a comparable age. A considerable number of these children had hearing defects, but on the whole, practically all the cases could be attributed to extracerebral causes and were unrelated to neonatal anoxia or convulsions. Davey considered that the role of prematurity had been overestimated and he regarded the basic pathological condition as needing clarification.

In the present material two of the hard of hearing patients who were neurologically normal had a BW below 1500 grams the third child was born at term.

a history of cerebral damage and in somewhat less than half of those who had not. Likewise, *Gottlieb* (1945) found EEG-abnormalities in about half his 67 children with b d. in the absence of organic cerebral damage. *Kennard* (1947) reported 65 per cent of abnormal EEG-records among a large series of children with b d. against 16 per cent in a comparable control material *Schlange* (1963) demonstrated a positive correlation between EEG-changes and specific b d a history of early brain damage and neurological abnormalities.

In the present material EEG-records were abnormal in two of the nine children who had b d (one also had seizures) In four EEG-records were normal and in three EEG had not been carried out.

5 Hearing defects

Impaired hearing was demonstrated in a total of eight patients, five of whom were among the severely handicapped in Group I (nos. 4 15 18 22, 28) The type of hearing loss could not be specified in these cases. Three patients with no persisting neurological features (nos. 38 39 and 40) had hearing loss for high frequencies only The literature contains several studies, pathological as well as clinical on hearing loss of this type.

Lewy and *Kobrak* (1936) demonstrated major structural differences between the dorsal and central cochlear nuclei and found the dorsal nucleus to be the only portion of the auditory pathways with a distinct separation of the fibres conducting high and low frequencies. The former are concentrated in the dorsal nucleus, which was considered to be particularly vulnerable being the phylogenetically younger portion of the cochlear nucleus, more vascular and less protected (*Craigie* 1938 and *H S Dunning* and *Wolf* 1937) Furthermore its structure is very complex.

Hall (1963) performed pathological studies on the auditory pathways in 50 newborn infants dying after pronounced asphyxia, as well as in 10 non-asphyxiated controls and in experimental animals (kittens) He found that no other part of the auditory pathways was as sensitive to hypoxia and exhibited such marked alterations as the cochlear nucleus

In comparable studies *Hall* (1965) found cell destruction to be greater in the dorsal than in the ventral portion of the cochlear nucleus.

In contrast, *Buch* (1966) inferred from histological examination of the inner ear of the newborn that lesions following birth injury would especially affect the labyrinth His series comprised 73 infants dying during the neonatal period (the majority being premature) and he found labyrinthine haemorrhages in 32 He thought that breech presentation, transverse presentation and forceps delivery were predisposing factors.

Fisch and *Osborn* (1954) performed audiometry on a large number of children with congenital hearing loss of various origin (morbus haemolyticus

had evidence of brain lesions, mainly following birth injury or severe asphyxia. He had no control series.

Kawi and Pasamanick (1959) who introduced the concept of "a continuum of reproductive casualties" felt that reading disorders were part of this continuum. They found, among dyslectics, a significantly higher incidence of pregnancy complications *than in a control series*, and moreover a *higher* though not statistically significant, incidence of neonatal abnormalities such as asphyxia, cyanosis and convulsion. Relatively more children with severe reading difficulties were found in the group with perinatal complications.

Prechtl (in *Money* Reading Disability 1962, p. 187) in a material of 50 children with behaviour disturbances and difficulties at school, found reading disorders in 45 (none of whom had exhibited neurological or psychiatric symptoms). All the patients also had choreatic twitching of face, tongue, neck and body and nearly all also had twitching of the eye muscles. In addition, more than half showed ambilaterality. In 50 per cent of the cases there had been complications *during pregnancy* and in 46 per cent neonatal disorders were reported. Prechtl suggested that some children would have reading difficulties because of inability to focus for long enough time associated with a short concentration span due to the choreatic activity. These functional deficiencies might further delay the development of cerebral dominance and of a function as complex as reading. He thought that minimal brain damage was a possible aetiology.

Zangwill (1960) found a history *of cerebral damage* or "minor epilepsy" to be fairly frequent in dyslectics. He suggested that individuals who were ambilateral or had a family history of ambilaterality might be especially prone to minimal brain lesions including birth injury and particularly likely to develop subsequent language disturbances (p. 25).

Critchley (1964 p. 17) cautioned against ascribing dyslexia to a focal brain lesion, because one would then have to ignore the important role played by *immaturity in* proportion to chronological age and cortical development. In any event delayed reading due to birth injury would, according to Critchley be entirely different from a specific dyslexia.

Ford (1960 p. 258) pointed out that no postmortem-studies have been *published and that it* is unknown whether a *developmental defect of the* cerebral cortex is present or not.

In spite of the fact that most authorities have ascribed dyslexia to dysfunction or immaturity *of the brain, the fundamental* aetiology remains obscure, and the possibility of perinatal complications as precipitating or causal factors has not been excluded. With this question still unresolved, the dyslectics in this *material* have been grouped together with the children exhibiting sequelae.

Congenital dyslexia in many respects resembles the later acquired disorder alexia. This fact has been an incentive in the search for a traumatic aetiology of the congenital disorder as well. However dyslexia is probably not a sharply defined clinical and aetiological entity but a more heterogenous condition. Even its demarcation has met with considerable difficulties, since a number of other reading defects must be excluded, viz those secondary to general mental retardation, visual or auditory defects, word deafness, speech disorders and emotional disturbances (cf *Hermann* 1955 *English edition* 1959) In view of the obvious familial factor and the co-existence of disturbances of language and lateralization, *Orton* (1925 general review 1937) ascribed dyslexia to defective or delayed development of unilateral cerebral dominance, and this theory has been supported by many writers (*Creak* 1936 and *Gallagher* 1950 among others) Most writers dealing with this condition emphasise the hereditary factor and consider dyslexia to be the result of cerebral dysfunction or delayed development, stressing to a lesser or greater degree the importance of disturbances of lateralization (see *Skydsgaard* 1942, *Hallgren* 1950 *Hermann* 1955 1959 *Drew* 1956, *Ettinger* 1962 and *Reinhold* 1963 among others)

Other workers do not exclude an organic factor *Hinshelwood* (1917) thought that cerebral damage of varying degree or cerebral dysfunction might give rise to varying degrees of dyslexia.

Eustis (1947) found the above mentioned symptoms in connection with a family history of clumsiness, and suggested that the cause of all the symptoms was delayed neuromuscular maturation due to slow myelinization.

Gesell and *Amatruda* (1947 p. 246) suggested that dyslexia could be a developmental manifestation of minimal cerebral damage, since developmental retardation might precede recovery from the injury They drew a parallel between behaviour disorders, speech difficulties and poorly developed unilateral dominance. A high correlation with minimal birth injury probably higher than generally recognized, was demonstrated.

Rabinovitch Drew De Jong Ingram and *Whitey* (1954) also suggested that dyslexia was part of a more generalized disturbance of integration, presumably a developmental dysfunction. They did not, however exclude the possibility of unrecognized minimal birth injury as an aetiological factor

Malmquist (1958) failed to find an increased incidence of birth trauma or natal abnormalities however his material showed a definite relationship with premature birth. In his opinion dyslexia was a variation within the normal range. In a very large group of children with reading difficulties analysed by *Eames* (1959) 1 4 per cent were found to present evidence of cerebral damage against 1 1 per cent in a control series of comparable size *Nicholls* (1960 and 1965) found that 2 per cent of children with dyslexia

Stillerman, Gibbs and *Perlstein* (1952) studied EEG-changes in children with squint. They demonstrated the presence of focal EEG-abnormalities in the occipital region in 74 per cent of children with cerebral palsy who had a squint and only in 38 per cent in c. p. children who had none. Similar EEG-changes were present in 20 per cent of a group of normal children with squint and in only 0.5 per cent in a group of controls. *Trojaborg* (1966, p. 41) could not reproduce this difference. He found occipital EEG-changes in some 15 per cent of c. p. children, whether squint was present or not.

EEGs had been carried out in 21 of the children with squint in the present material. 13 were normal and 8 abnormal however only one of these (no. 30) had changes in the occipital region.

I. *Electroencephalography*

The number of available EEG-studies is too small to allow an estimation of the incidence of EEG-abnormalities. Of 40 recordings 17 were abnormal (13 in Group I, 4 in Group II, none in Groups III and IV) and 23 were normal (8 in Group I, a total of 15 in Groups II, III and IV).

The same reservation applies to the following studies. At a follow-up of 201 children with evidence of neonatal intracranial damage, or asphyxia, *Mørstad* and *Kaada* (1953) carried out EEG studies on 54 patients and found abnormalities in 37 Among these one patient had developed normally the remainder had epilepsy mental retardation or cerebral palsy *D'Avignon* and *Kellson* (1953) carried out an EEG-follow-up in 44 out of 61 children with a history of neonatal asphyxia. One third, all exhibiting cerebral symptoms, had severely abnormal tracings. The records of a further third showed minor dysrhythmia, and a third were normal. The children in the last two groups were clinically normal. The authors emphasized that the slight dysrhythmia might be due to cerebral damage to a certain degree, but that EEG-abnormalities could also be seen in normal subjects. The frequency of mild dysrhythmia in normal children is estimated as follows. *Perlstein, Gibbs* and *Gibbs* (1947) 16 per cent; *Polacek et al.* (1965) 11.6 per cent; *Brandt, Brandt* and *Vollmond* (1961) 6 per cent (of 120 normal children below the age of 15)

7 *Squint*

Squint was found in 30 patients or 20 per cent of all survivors of the neonatal period. This is in line with *Rydberg's* finding (1932) in a series of children presenting severe cerebral symptoms during the neonatal period (25 per cent)

The incidence of squint in a normal population is estimated to be about one or two per cent, somewhat higher in childhood. *Thomsen* (1924) found 3 per cent in children aged 5 to 6 1 6 per cent in the age group 12 to 13 *McNeil* (1955) reported 2 7 per cent (age 5 to 15) *Frandsen* (1960) and *Millar* (1965) both found 4.5 per cent.

In the present material about half the patients with a squint were found in the group of 29 patients with severe cerebral sequelae (incidence 51 per cent) It is well known that squint is commonplace in children with cerebral palsy *Guibor* (1953) observed a squint in 60 per cent of his material of children with cerebral palsy *Plum* (1956) in a series of 543 children with cerebral palsy found an incidence ranging from 23 to 72 per cent, lowest in spastic hemiplegics, highest in patients with athetosis due to neonatal jaundice. In patients with quadriplegia and ataxia the rate was about 50 per cent. *Douglas* (1961) in a comparable material of 168 patients, observed a frequency of 45 to 47 per cent, rising from 33 to 58 with increasing severity of handicaps including mental deficiency

Moreover it has been demonstrated that squint is more frequent in mentally defectives than in children of normal intelligence Thus *Frandsen* (1960) found a squint to be present in 12.4 to 24.3 per cent of children attending schools for mentally defectives, and in 33 per cent of children in an institution for mentally defectives.

In the Groups II–IV of the present series (124 patients with minor or no handicap) 15 children had a squint (12 per cent) i. e. a higher incidence than in a group of normal children and lower than in a group with severe cerebral defect. Even excluding the six children who had a family history of squint the frequency is still at the upper normal limit (7 per cent)

Squint is not an aetiological entity and it is not always possible to establish its origin. A survey of aetiological possibilities has been made by *Frandsen* (1960) among others.

The higher incidence of squint in children with diverse cerebral defects supports the likelihood of a common aetiology in these patients. It may be added that higher incidence of squint has also been demonstrated in children with symptomatic epilepsy viz. 13 per cent in children of normal intelligence, 28 per cent in mentally defectives and 37 per cent in children with a history of birth injury (*Millar* 1965)

Monosymptomatic squint in this material was found only in two patients (in Group III) one of whom had a familial predisposition.

cyanosis 2 respiratory abnormalities 3 flaccidity convulsions 5 tremor 6 irritability 7 rigidity

Fig. 3

Incidence of neonatal symptoms in 122 patients dying in the neonatal period, the main causes of death being

1. pulmonary atelectasis (normal brain).
2. pulmonary atelectasis and cerebral oedema.
3. pulmonary atelectasis, intracranial haemorrhage ± cerebral oedema.
4. intracranial haemorrhage ± cerebral oedema (normal lungs).

CHAPTER III

The diagnostic significance of neonatal symptoms based on autopsy findings in patients dying in the neonatal period

The 122 patients who died neonatally were, as already mentioned, classified according to the principal cause of death as revealed by postmortem examination viz 1) pulmonary atelectasis, normal brain, 2) pulmonary atelectasis and cerebral oedema, 3) pulmonary atelectasis and cerebral haemorrhage ± cerebral oedema, and 4) cerebral haemorrhage ± cerebral oedema, normal lungs.

The following analysis aims at demonstrating differences in the symptomatology of the respective groups that would make it possible to distinguish clinically between infants with cerebral damage and infants with normal brains.

Fig. 3 shows the frequency of each symptom within the four groups.

The most striking feature is the total absence of convulsion tremor irritability and rigidity in Group 1

Because of the small size of this group it has been supplemented as follows. 1) all infants dying neonatally at the DPGe from 1957 to 1964 who were found at autopsy to have pulmonary atelectasis and normal brain, a total of 16 cases 2) a total of 10 infants dying neonatally at the University Hospital (Rigshospitalet = RH) from 1961 to 1964 in whom autopsy performed at the Department of Pathology of the RH had revealed pulmonary atelectasis as the sole pathological abnormality Informations were extracted from the clinical records of these children similarly to those of the original material. The clinical data on infants dying at the RH were obtained from the records of the Departments of Obstetrics A and B where the infants had been admitted and seen by paediatricians.

This enlarged the series to the more acceptable total of 46 cases, though the group of mature infants remained very small and the preponderance of premature became even larger The outcome is given in Fig. 4 The fact that this enlarged group also failed to exhibit convulsion tremor irritability and rigidity supports the theory of a specific cerebral origin for these symptoms. In all other groups they occurred with fairly consistent frequency

As seen from Fig. 3 the frequency of each symptom is essentially the

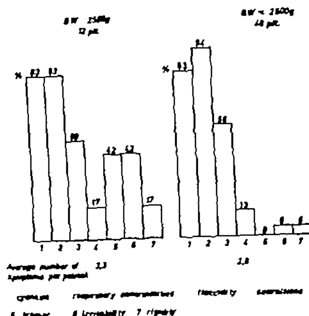


Fig. 5

Incidence of neonatal symptoms in the enlarged material comprising 60 patients dying in the neonatal period, the main causes of death being pulmonary atelectasis and cerebral oedema.

Even though the symptoms of convulsion, tremor, irritability and rigidity seem to be specific to cerebral damage, several patients may have brain damage, perhaps proving fatal, without exhibiting any of these symptoms.

TABLE 11

The time of onset of convulsion in 102 (143) patients dying neonatally and exhibiting pathological findings on brain section

(Figures in parenthesis indicate enlarged material)

Autopsy findings	No. pat.	No. of patients with convulsions	
		From 1st day	Only after 1st day
Cerebral oedema + pulmonary atelectasis	19 (60)	1 (2)	2 (6)
Cerebral haemorrhage ± oedema + pulmonary atelectasis	61	7	7
Cerebral haemorrhage ± oedema, normal lungs	22	4	2
Total	102 (143)	12 (13)	11 (15)

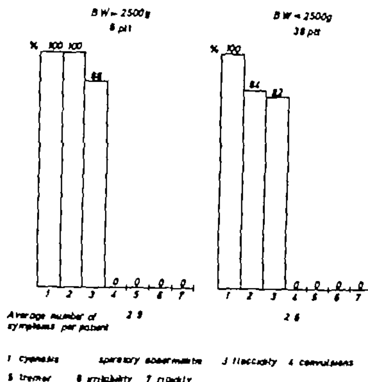


Fig 4

Incidence of neonatal symptoms in the enlarged material comprising 46 patients dying in the neonatal period, the main cause of death being pulmonary atelectasis.

same in the group with cerebral oedema as in those with cerebral haemorrhage ± cerebral oedema. Here, too the former group was very small and consequently was enlarged—in the same manner as mentioned above—by including 29 patients from DPGe and 12 patients from the obstetric departments A and B and the Dept. of Pathology at the RH Brain section was performed by Dr Inge Tygstrup. The group then amounted to 60 infants, of whom 12 were mature. The distribution of the symptoms can be seen in Fig 5 Making allowance for the small number of mature patients the trend is unchanged, with the same symptoms occurring with equal frequency in cases with cerebral oedema and in those with cerebral haemorrhage.

The time of onset of convulsions is of no particular help in making a differential diagnosis because of the rarity of this symptom in the group (see Table 11) In cases with cerebral haemorrhage about half the convulsions started within the first 24 hours of birth the remainder did not begin until the second day or later When cerebral oedema occurred in the absence of haemorrhage, there was a tendency towards late onset, however in some cases the convulsion did in fact begin on the first day

Among the 50 full-term infants with cerebral damage 23 or 46 per cent, had presented only cyanosis, respiratory disorders and flaccidity in varying combinations. The corresponding figures in premature infants with cerebral damage were 41 or 79 per cent.

As seen from Table 12 this relationship is essentially the same whether cerebral oedema or cerebral haemorrhage is present. A substantial proportion of these children, notably among the premature, will present the same symptoms as those dying from pulmonary atelectasis.

The question is, therefore, whether it is possible to make a clinical distinction between the two groups.

The form in which cyanosis occurs seems to offer a guide. In Table 13 the three groups presenting pathological brain findings have been listed together. Cyanotic attacks seem to be somewhat more frequent among the patients with cerebral damage; however since this form is seen frequently also in the absence of cerebral damage, it is of no diagnostic value. The same may be said "with opposite signs" of permanent cyanosis, which is more frequent in isolated pulmonary atelectasis.

If, however the time of onset of cyanotic attacks is considered—whether occurring during the first 24 hours of birth or not until the second day of life or later—a difference becomes evident (Table 14) Delayed onset of cyanotic attacks is seen only in cases with cerebral damage and was observed in about one-fifth of that group.

Similarly a comparison has been made between cyanosis in mature and premature infants as well as between infants with cerebral oedema and with cerebral haemorrhage. No differences were demonstrated (see Tables 15 16 and 17) with the exception of a preponderance of cyanotic attacks of early

TABLE 15

Forms of cyanosis in 122 (189) patients dying in the neonatal period. Patients are grouped according to BW

(Figures in parentheses indicate the enlarged series)

Autopsy findings		No. pat.	Cyanotic attacks	Permanent cyanosis
BW > 2500 g	Pulmonary atelectasis Normal brain	5 (8)	2 (5) pat.	3 (3) pat.
	Pathological brain ± pulmonary atelectasis	50 (53)	62 % (62 %)	22 % (21 %)
BW < 2500 g	Pulmonary atelectasis Normal brain	15 (38)	40 % (37 %)	60 % (63 %)
	Pathological brain ± pulmonary atelectasis	52 (90)	50 % (55 %)	37 % (28 %)

TABLE 12

Neonatal symptoms in 102 infants dying neonatally with pathological findings at brain section

Autopsy findings	BW > 2500 g		BW < 2500 g		Total
	Without specific symptoms	With specific symptoms	Without specific symptoms	With specific symptoms	
Pulm. atelectasis + cerebral oedema	4	5	9	1	19
Pulmonary atelectasis + cerebral haemorrhage ± cerebral oedema	13	14	25	9	61
Cerebral haemorrhage ± cerebral oedema, normal lungs	6	8	7	1	22
Total	23	27	41	11	102

TABLE 13

Forms of cyanosis in 122 (189) infants dying during the neonatal period
(Figures in parentheses indicate the enlarged material)

Autopsy findings	No. pat.	Cyanotic attacks	Permanent cyanosis
Pulmonary atelectasis normal brain	20 (46)	40 % (41 %)	60 % (59 %)
Pathological brain ± pulmonary atelectasis	102 (143)	56 % (57 %)	27 % (25 %)

TABLE 14

The time of onset of cyanotic attacks in 122 (189) patients dying in the neonatal period
(Figures in parentheses indicate the enlarged group)

Autopsy findings	No. pat.	Cyanotic attacks	
		From 1'st day	Late occurrence only
Pulmonary atelectasis normal brain	20 (46)	40 % (41 %)	0 (0)
Pathological brain ± pulmonary atelectasis	102 (143)	35 % (29 %)	21 % (28 %)

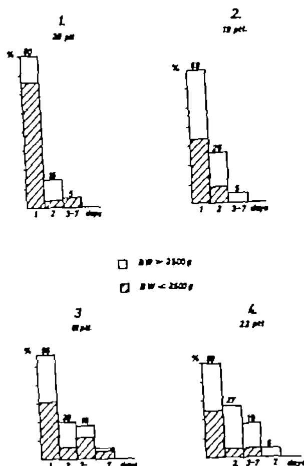


Fig. 6
Time of neonatal death in 122 patients. 1–4 diagnostic groups as in Fig. 3, p. 59

Here, too, the average number of symptoms per patient was somewhat higher in the mature than in the premature, though with little variation between the respective pathological groups (Figs. 3 4 and 5)

Conclusion

The diagnosis of cerebral damage in newborn infants is difficult to establish, particularly in the premature, who exhibit very few symptoms.

Convulsion, tremor irritability and rigidity can, with a degree of certainty be considered specifically cerebral symptoms, being found in the present material only in patients who were found to have cerebral haemorrhages

TABLE 16

Time of onset of cyanotic attacks in 122 (189) patients dying in the neonatal period. Patients grouped according to BW

(Figures in parentheses indicate the enlarged series)

Autopsy findings		No. pat.	Cyanotic attacks	
			From 1'st day	Lat occur rence only
BW > 2500 g	Pulmonary atelectasis Normal brain	5 (8)	2 (5) pat.	0 (0) pat.
	Pathological brain ± pulmonary atelectasis	50 (53)	34 % (34 %)	28 % (28 %)
BW < 2500 g	Pulmonary atelectasis Normal brain	15 (38)	40 % (37 %)	0 (0) pat.
	Pathological brain ± pulmonary atelectasis	52 (90)	37 % (27 %)	13 % (28 %)

TABLE 17

Form of cyanosis and time of onset of cyanotic attacks in the enlarged series of 143 patients dying in the neonatal period and revealing pathological findings on brain section

Autopsy findings	No. pat.	Cyanotic attacks	Permanent cyanosis
Cerebral oedema	60	57 %	27 %
Cerebral haemorrhage ± oedema	83	59 %	24 %

	No. pat.	Cyanotic attacks	
		From 1'st day	Late occur rence only
Cerebral oedema	60	23 %	33 %
Cerebral haemorrhage ± oedema	83	34 %	24 %

onset in cerebral haemorrhage and delayed onset in cerebral oedema, a trend with no obvious practical implications.

Permanent cyanosis in all cases developed within 24 hours of birth.

The large majority of neonatal fatalities occurred within 24 hours of birth, more often in cases with isolated pulmonary atelectasis. In cases of cerebral haemorrhage the patients survived somewhat longer with about one quarter dying later than the third day and some as late as the second week of life. Only a small percentage in the groups with pulmonary atelectasis and with pulmonary atelectasis as well as cerebral oedema survived the third day and one survived the first week. (See Fig. 6)

CHAPTER IV

The significance of neonatal symptoms in the immediate prognosis

In the following pages an attempt is made to detect neonatal symptoms or groups of symptoms that may offer a clue to the prognosis for immediate survival.

Fig. 7 illustrates the incidence of individual symptoms in the infants who survived the neonatal period compared with those who died.

It is evident that in the entire group as well as in the two weight groups an appreciable majority of the patients who died exhibited cyanosis, respiratory disorder and flaccidity In this respect there is no difference between mature and premature infants.

The remaining symptoms are slightly more frequent in the survivors than in the infants who died, whether mature or premature. Here again the mature, whether surviving or not, exhibited more of these symptoms than the premature.

The average number of symptoms per patient was somewhat lower in the survivors, viz. 2.5 in the mature compared with 3 1 in those who died. The corresponding figures for the premature were 1 7 and 2.5 Thus on average the premature in each group presented fewer symptoms than the mature.

Cyanosis the commonest symptom, was present in 208 patients. Half of these survived prematurity however plays an important role, since 74 per cent of the premature and only 36 per cent of the mature with cyanosis died during the neonatal period (see Table 18) This table also shows the mortality rates for the different forms of cyanosis subdivided according to time of onset and duration.

Permanent cyanosis persisting beyond the first few hours of life seems to indicate a poor prognosis for survival in mature as well as premature patients.

Cyanotic attacks occurred in 77 per cent of the cases, somewhat more often in the mature. Its occurrence during the first day of life apparently is a less favourable sign in the premature than in the mature.

or cerebral oedema at autopsy These symptoms were rare in the premature infants.

Brain damage may be present in a large number of cases, especially among the premature, in which cyanosis, respiratory disorder or flaccidity are the only clinical features

The onset of cyanotic attacks after the first 24 hours of life suggests cerebral damage.

Clinical findings are not conclusive in differentiating between cerebral oedema and cerebral haemorrhage.

The principal point at which the above conclusion diverges from that of previous authors concerns the statement that convulsion, tremor irritability and rigidity are specific cerebral symptoms. Many authors (*Clein* 1929 *Grulee* 1936 *Liebe* 1940 *Peterman* 1946 *Bound* 1956 *Illingworth* 1957 *Ahvenainen* 1956–59 and *Craig* 1960) have found convulsion in extra-cerebral conditions, although it was reported to be more frequent in cerebral disorders (*Peterman* 1946 *Ahvenainen* 1958 and *Craig* 1960) The main reason for this discrepancy may be the method of selection in the present study which excludes in advance many conditions that may cause convulsion.

Otherwise the results are in agreement with those of previous writers. This applies to the general difficulties in establishing a definite diagnosis as well as the impossibility of distinguishing clinically between cerebral oedema and cerebral haemorrhage (*Seitz* 1907 *Esch* 1916 and *Craig* 1960) The relative scarcity of specifically cerebral symptoms in the premature is also in accord with the findings of previous authors (*Heidler* 1927 *Bound* 1956 *Znamenacek* 1957 and *Craig* 1960)

TABLE 18

Forms of cyanosis and mortality in 208 newborn infants

Cyanosis	Total	131 patients BW > 2500 g		77 patients BW < 2500 g	
		Survi-vors	Neonatal deaths	Survi-vors	Neonatal deaths
Permanent, a few hours	8	7	1	0	0
Permanent, within 1'st day	38	2	12	0	24
Permanent, 1 st and following days	2	0	1	0	1
Attacks, 1'st day	84	37	14	9	24
Attacks, 1'st and following days	38	27	5	5	1
Attacks, later than 1'st day only	38	11	14	6	7
Total	208	84	47 (36 %)	20	57 (74 %)

Delayed onset of cyanotic attacks, i. e. after the first 24 hours of life, seems, in the mature, to imply a worse prognosis than earlier onset.

Cyanosis here has been considered on its own. It must, however, be borne in mind that in the great majority of cases this feature was accompanied by other symptoms.

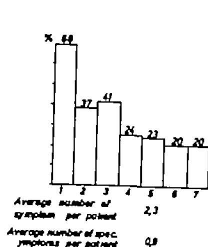
As already mentioned, 22 patients presented cyanosis as the only symptom. As seen from Table 19, monosymptomatic cyanosis always was attack-wise, and three of the 22 patients died neonatally. The mortality rate is equal in the two weight groups, and considerably lower than in the group with cyanosis in combination with other symptoms. In the latter group, which comprises 186 patients (208 minus 22), the mortality rate among the mature was 39 per cent, in the premature the rate was 80 per cent.

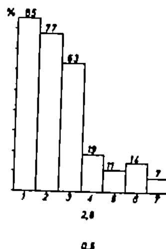
Respiratory abnormalities were present, as the next commonest feature, in 152 patients, of whom only three had no additional symptoms. All three were born at term, none had periodic apnoea, all survived the neonatal period. The mortality rate among the remaining 149 patients, who had

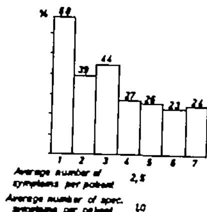
TABLE 19

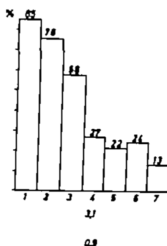
Monosymptomatic cyanosis in 22 newborn patients

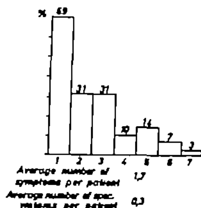
Cyanosis	Total	BW > 2500 g		BW < 2500 g	
		Survi-vors	Neonatal deaths	Survi-vors	Neonatal deaths
Permanent	0	0	0	0	0
Attacks, first day	14	9	2	2	1
Attacks, 1 st & following day	4	3	0	1	0
Attacks, later than 1 st day only	4	1	0	3	0
Total	22	13	2	6	1

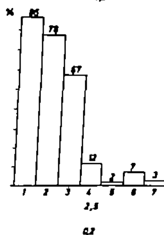












1 cyan sis 2 spiratory abnormalities 3 flaccidity 4 convulsion 5 tremor 6 irritability 7 rigidity

Fig 7

Incidence of neonatal symptoms in patients surviving (left column) and dying during the neonatal period (right column).
Upper part: the total material.
Middle: patients with BWs over 2500 grams.
Lower part: patients with BWs below 2500 grams.

TABLE 22

Convulsion in 58 newborn patients presenting additional symptoms

Convulsion	Total	BW > 2500 g		BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
During first day	19	9	6	0	4
During 1'st and following days	9	7	2	0	0
Only after first day	30	16	7	3	4
Total	58	32	15 (32 %)	3	8 (73 %)

The onset of convulsion, whether occurring within the first 24 hours of life or later apparently had no bearing on the immediate prognosis in the mature. The number of premature infants is too small to allow conclusions.

Two mature patients had convulsions as the only symptom. The onset was delayed. Both survived the neonatal period.

Tremor irritability and *rigidity* occurred equally in the survivors and those dying in the neonatal period of both weight groups. The number of *premature patients presenting these symptoms was too small to be prognostically conclusive.*

In the mature patients, of whom about 40 exhibited each of the three symptoms, the neonatal mortality rate was 20–30 per cent, or somewhat lower than for the aforesaid symptoms.

Neither tremor nor rigidity occurred on their own. Irritability was present as the only symptom in two full-term infants, one of whom died neonatally

Combinations of symptoms were numerous however as might be expected,

TABLE 23

Mortality rates in newborn patients with non-specific symptoms only

Neonatal symptoms	No	% of all 275 pat.	BW > 2500 g			BW < 2500 g		
			Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir disorder	47	17 %	11	13	54 %	5	18	78 %
Cyanosis + flaccidity	23	8 %	10	2	17 %	2	9	82 %
Respir disorder + flaccidity	5	2 %	1	1	(50 %)	0	3	(100 %)
Cyanosis + respir disorder + flaccidity	49	18 %	14	10	42 %	1	24	96 %
	124	45 %	36	26		8	54	
			62 = 35 % of 179			62 = 65 % of 96		

TABLE 20

Respiratory disorders in 149 newborn infants presenting additional symptoms

Respiratory disorder	Total	87 patients BW > 2500 g		62 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Difficult, grunting	97	39	22	10	26
Periodic apnoea	33	6	14	0	13
Difficult, grunting and periodic apnoea	19	0	6	0	13
Total	149	45	42 (48 %)	10	52 (84 %)

additional symptoms, was 63 per cent, higher in the premature (84 per cent) than in the mature (48 per cent) the difference between the weight groups was much the same as in the cyanotic patients, though with a relatively higher mortality in the mature.

The respiratory disorders consisted of either difficult, grunting and somewhat irregular respiration as the most common form in each weight group or of periodic apnoea or both.

As may be seen from Table 20 periodically apnoeic respiration or respiration that was also difficult suggested an unfavourable prognosis for life in mature as well as in premature patients. Grunting respiration on its own appeared to be a more ominous sign in the premature than in the mature.

Flaccidity which was next in frequency occurred in 140 patients, or in about half of both weight groups As an isolated symptom it was present in 8 patients, or four in each group Of these one premature infant died. In the remaining 132 cases 39 per cent of the mature and 88 per cent of the premature died (Table 21) The figures thus parallel those found for the two aforesaid symptoms.

Convulsion was present in 60 patients. As already mentioned its frequency was equal in surviving and fatal cases within the two weight groups. In the premature, convulsion when occurring with other symptoms, was associated with a mortality rate as high as 73 per cent as against 32 per cent in the mature (see Table 22)

TABLE 21

Flaccidity in 132 newborn patients presenting additional symptoms

	Total	82 patients BW > 2500 g		50 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Flaccidity	132	50	32 (39 %)	6	44 (88 %)

TABLE 22

Convulsion in 58 newborn patients presenting additional symptoms

Convulsion	Total	BW > 2500 g		BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
During first day	19	9	6	0	4
During 1st and following days	9	7	2	0	0
Only after first day	30	16	7	3	4
Total	58	32	15 (32 %)	3	8 (73 %)

The onset of convulsion, whether occurring within the first 24 hours of life or later apparently had no bearing on the immediate prognosis in the mature. The number of premature infants is too small to allow conclusions.

Two mature patients had convulsions as the only symptom. The onset was delayed. Both survived the neonatal period.

Tremor irritability and rigidity occurred equally in the survivors and those dying in the neonatal period of both weight groups. The number of premature patients presenting these symptoms was too small to be prognostically conclusive.

In the mature patients, of whom about 40 exhibited each of the three symptoms, the neonatal mortality rate was 20–30 per cent, or somewhat lower than for the aforesaid symptoms.

Neither tremor nor rigidity occurred on their own. Irritability was present as the only symptom in two full-term infants, one of whom died neonatally

Combinations of symptoms were numerous· however as might be expected,

TABLE 23

Mortality rates in newborn patients with non-specific symptoms only

Neonatal symptoms	No.	% of all 275 pat.	BW > 2500 g			BW < 2500 g		
			Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir disorder	47	17 %	11	13	54 %	5	18	78 %
Cyanosis + flaccidity	23	8 %	10	2	17 %	2	9	82 %
Respir disorder + flaccidity	5	2 %	1	1	(50 %)	0	3	(100 %)
Cyanosis + respir disorder + flaccidity	49	18 %	14	10	42 %	1	24	96 %
	124	45 %	36	26		8	54	
			62 = 35 % of 179			62 = 65 % of 96		

TABLE 20

Respiratory disorders in 149 newborn infants presenting additional symptoms

Respiratory disorder	Total	87 patients BW > 2500 g		62 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Difficult, grunting	97	39	22	10	26
Periodic apnoea	33	6	14	0	13
Difficult, grunting and periodic apnoea	19	0	6	0	13
Total	149	45	42 (48 %)	10	52 (84 %)

additional symptoms, was 63 per cent, higher in the premature (84 per cent) than in the mature (48 per cent) the difference between the weight groups was much the same as in the cyanotic patients, though with a relatively higher mortality in the mature.

The respiratory disorders consisted of either difficult, grunting and somewhat irregular respiration as the most common form in each weight group or of periodic apnoea or both.

As may be seen from Table 20 periodically apnoeic respiration or respiration that was also difficult suggested an unfavourable prognosis for life in mature as well as in premature patients Grunting respiration on its own appeared to be a more ominous sign in the premature than in the mature.

Flaccidity which was next in frequency occurred in 140 patients, or in about half of both weight groups. As an isolated symptom it was present in 8 patients, or four in each group. Of these one premature infant died. In the remaining 132 cases 39 per cent of the mature and 88 per cent of the premature died (Table 21) The figures thus parallel those found for the two aforesaid symptoms.

Convulsion was present in 60 patients As already mentioned its frequency was equal in surviving and fatal cases within the two weight groups In the premature, convulsion, when occurring with other symptoms, was associated with a mortality rate as high as 73 per cent as against 32 per cent in the mature (see Table 22)

TABLE 21

Flaccidity in 132 newborn patients presenting additional symptoms

	Total	82 patients BW > 2500 g		50 patients BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
Flaccidity	132	50	32 (39 %)	6	44 (88 %)

TABLE 22

Convulsion in 58 newborn patients presenting additional symptoms

Convulsion	Total	BW > 2500 g		BW < 2500 g	
		Survivors	Neonatal deaths	Survivors	Neonatal deaths
During first day	19	9	6	0	4
During 1st and following days	9	7	2	0	0
Only after first day	30	16	7	3	4
Total	58	32	15 (32 %)	3	8 (73 %)

The onset of convulsion, whether occurring within the *first* 24 hours of life or later apparently had no bearing on the immediate prognosis in the mature. The number of premature infants is too small to allow conclusions.

Two mature patients had convulsions as the only symptom. The onset was delayed. Both survived the neonatal period.

Tremor irritability and *rigidity* occurred equally in the survivors and those dying in the neonatal period of both weight groups. The number of premature patients presenting these symptoms was too small to be prognostically conclusive.

In the mature patients, of whom about 40 exhibited each of the three symptoms, the neonatal mortality rate was 20–30 per cent, or somewhat lower than for the aforesaid symptoms.

Neither tremor nor rigidity occurred on their own. Irritability was present as the only symptom in two full-term infants, one of whom died neonatally

Combinations of symptoms were numerous however as might be expected,

TABLE 23

Mortality rates in new-born patients with non-specific symptoms only

Neonatal symptoms	No.	% of all 275 pat.	BW > 2500 g			BW < 2500 g		
			Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir disorder	47	17 %	11	13	54 %	5	18	78 %
Cyanosis + flaccidity	23	8 %	10	2	17 %	2	9	82 %
Respir disorder + flaccidity	5	2 %	1	1	(50 %)	0	3	(100 %)
Cyanosis + respir disorder + flaccidity	49	18 %	14	10	42 %	1	24	96 %
	124	45 %	36	26		8	54	
			62 = 35 % of 179			62 = 65 % of 96		

TABLE 24

Mortality rates in newborn infants presenting two or three non-specific symptoms co-existent with one or more additional symptoms

Neonatal symptoms	No.	BW > 2500 g			BW < 2500 g		
		Survivors	Neonatal deaths	Mortality %	Survivors	Neonatal deaths	Mortality %
Cyanosis + respir disorder	82	27	24	47 %	3	28	90 %
Cyanosis + flaccidity	82	29	24	45 %	3	26	90 %
Respir disorder + flaccidity	76	22	23	51 %	3	28	90 %
Cyanosis + respir disorder + flaccidity	18	6	10	63 %	1	1	(50 %)

the commonest included cyanosis, respiratory disorder and flaccidity Table 23 shows the mortality rate in the cases where these symptoms occurred in the absence of specific cerebral symptoms. 45 per cent of all the 275 patients belonged in these groups, considerably more (65 per cent) premature than mature infants (35 per cent) Table 24 gives mortality rates for the same combinations co-existent with other symptoms.

Conclusion

As might be expected permanent cyanosis persisting for more than a few hours and periodic apnoea are unfavourable omens for survival in mature as well as premature infants.

Cyanotic attacks within the first 24 hours of life, difficult and grunting respiration, flaccidity and convulsion are also of serious prognostic significance in the premature newborn, but less so in the mature. Combinations of the non-specific features. cyanosis, respiratory disorder and flaccidity are also poor prognostic signs in premature infants.

In mature neonates the onset of cyanotic attacks after the first day of life implies a more unfavourable prognosis than onset within the first 24 hours.

The specific cerebral symptoms—convulsion, tremor irritability and rigidity—with the exception of convulsions in the premature, seem to have less serious implications for the immediate prognosis.

An increasing number of symptoms means a decreasing chance of survival However death occurred in mature as well as premature infants who presented only one neonatal symptom.

CHAPTER V

The significance of neonatal symptoms in long term prognosis

The eventual progress of the surviving children as already mentioned differed greatly In the following pages a comparison is made between neonatal symptoms in those infants who later exhibited severe, minor or possible cerebral sequelae and those who developed normally The aim has been the assessment of possible symptomatological differences during the neonatal period that might give a reliable indication of the long-term prognosis.

Fig. 8 shows the incidence of neonatal symptoms in mature and premature patients in the Groups I–IV presented in Chapter II (divided according to decreasing degrees of severity with Group IV being normal)

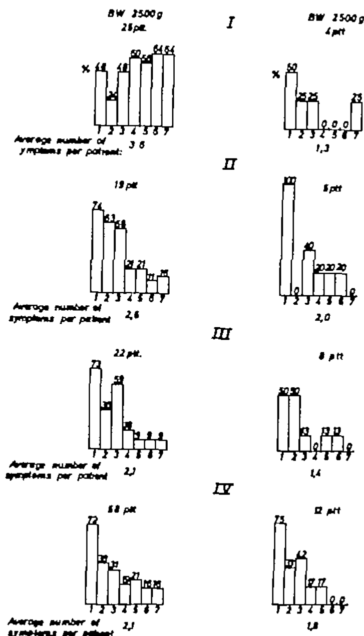
Since the premature groups are very small, all calculations concerning these groups must be treated with reservation.

The most conspicuous difference is the higher incidence of convulsion, tremor irritability and rigidity in the mature infants in Group I compared with all other groups. 23 patients, or 92 per cent in this group exhibited one or more of these symptoms. The corresponding percentage for mature children in the other groups was about 40· in the premature groups the overall percentage was about 25

The average number of symptoms per patient decreased gradually from Groups I to IV being, respectively 3.6, 2.6, 2.1 and 2.1 In the premature the figures, without showing distinctive trends, were lower viz. 1.3 2.0, 1 4 and 1 8 symptoms per patient, respectively

The symptomatological combinations were so numerous that the same combination occurred only in few cases. An attempt to establish the prognosis for all combinations would have practically decimated the material. The approach has been as follows.

1) to determine whether any one symptom occurring on its own might give definite indications of the long-term prognosis, and subsequently to similarly evaluate groups of patients exhibiting a combination of
2) two or three non-specific symptoms,
3) one non-specific and one specific symptom,
4) two specific symptoms.



1. cyanosis 2 respiratory abnormalities 3 flaccidity 4. convulsions 5 tremor 6. irritability 7 rigidity

Fig 8

Incidence of neonatal symptoms in patients surviving the neonatal period.

I Patients with severe cerebral sequelae.
II Patients with minor cerebral sequelae.
III Patients with mild deviations of presumably cerebral origin.
IV Patients with later normal development.

Finally an evaluation has been made of those children who presented the same symptoms as those in the last three groups in combination with one or more additional symptoms.

1 *Patients with only one neonatal symptom*

As already mentioned a single symptom was found in 37 patients. Of these 32 survived the neonatal period. Table 25 shows their later fate. The groups are small and allow no definite conclusions. However, it should be noted that the specific symptoms seldom occurred on their own, and not at

TABLE 25

The relationship between neonatal symptoms and later condition in the presence of one symptom only

Neonatal symptoms	BW > 2500 23 patients					Follow-up groups	BW < 2500 g 9 patients			
	Total	I	II	III	IV	Total	I	II	III	IV
Cyanosis	13	1		2	10	6	1	2	1	2
Respir. disorder	3		2		1	0				
Flaccidity	4		1	2	1	3			1	2
Convulsion	2	1			1	0				
Irritability	1			1		0				
Pat. with only one non-specific sympt.	20	5 %	15 %	20 %	60 %					
All pat. regardless of BW with 1 non-specific sympt. only	29	7 %	17 %	21 %	55 %					

TABLE 26

Relationship between neonatal symptoms and later condition in the presence of two or three non-specific symptoms

Neonatal symptoms	BW > 2500 g 36 patients					Follow-up groups	BW < 2500 8 patients			
	No	I	II	III	IV	No.	I	II	III	IV
Cyanosis + respir. disorder	11		3		8	5	1		2	2
Cyanosis + flaccidity	10	1	2	2	5	2		2		
Respir. disorder + flaccidity	1				1	0				
Cyanosis + respir. disorder + flaccidity	14		4	7	3	1				1
BW > 2500 g	36	3 %	25 %	25 %	47 %					
All patients in both weight groups	44	5 %	25 %	25 %	45 %					

all in the premature. Convulsion as well as irritability were found on their own in a few mature children, and were not invariably indicative of a poor prognosis. Cyanosis, which was the commonest single symptom, most often implied a favourable prognosis.

2. *Patients with two or three non specific symptoms*

The later fate of infants showing two or three non specific symptoms apparently did not differ from those who exhibited only one unspecific symptom (see Tables 25 and 26) The distribution within Groups I–IV in the latter group taken as a whole, was 7 17 21 and 55 per cent and in the former 5 25 25 and 45 respectively

3 *Patients with one specific and one non-specific symptom*

This combination was found in only a small number of cases. Table 27 gives the figures, from which it can be seen that the presence of one specific plus one non-specific symptom from a prognostic point of view equals the presence of non-specific symptoms only

TABLE 27

Relationship between neonatal symptoms and later condition in the presence of one specific plus one non specific symptom

Neonatal symptoms	BW > 2500 g 8 patients					BW < 2500 g 3 patients				
	Follow-up groups									
	No.	I	II	III	IV	No.	I	II	III	IV
Convulsion + cyanosis	3			2	1	1				1
Convulsion + flaccidity	1		1							
Tremor + cyanosis					2	1				1
Irritability + respir disorder	0					1			1	
Irritability + flaccidity	1	1				0				
Rigidity + cyanosis	1				1	0				
All patients in both weight groups	11	1	1	3	6					

4 *Patients with two specific symptoms*

This combination was seldom found in the mature and not at all in the premature (see Table 28) The figures do not allow any conclusion to be drawn but suggest a tendency towards a more unfavourable prognosis three of the eight patients are found in Group I however the likelihood of a normal development exists.

These four groups comprise well over half the mature (75) and about two-thirds (20) of the premature infants surviving the neonatal period.

TABLE 28

The relationship between neonatal symptoms and later condition in the presence of two specific symptoms

Neonatal symptoms	BW > 2500 g 8 patients Follow-up groups				
	No.	I	II	III	IV
Convulsion and tremor	1	1			
Convulsion and rigidity	3	1		2	
Tremor and irritability	2				2
Tremor and rigidity	1	1			
Irritability and rigidity	1				1
Total	8	3	0	2	3

In the following, consideration is given to those patients who presented the same combinations of symptoms as the last three groups plus one or more additional features, whether specific or not.

Table 29 illustrates the relationship between later condition and the presence of no less than three neonatal symptoms, of which at least two are non-specific. A comparison with Table 26, where only two or three non-specific symptoms were present, suggest that the risk of a more unfavourable course increases proportionally with the number of symptoms.

TABLE 29

Relationship between neonatal symptoms and later condition in the presence of two or three non-specific symptoms plus one or more additional symptoms

Neonatal symptoms	BW > 2500 g					BW < 2500 g				
	Follow-up groups									
	No.	I	II	III	IV	No.	I	II	III	IV
Cyanosis + respir disorder	27	4	7	8	8	3			1	2
Cyanosis + flaccidity	29	5	6	9	9	3				3
Flaccidity + respir disorder	22	3	6	7	6	3	1			2
Cyanosis + respir disorder + flaccidity	6	2	2		2	1				1
BW > 2500 g		15–20 %			30 %					

Table 30 lists combinations of one specific, one non-specific together with at least one additional symptom. A comparison with Tables 27 and 29 reveals that in the presence of at least three symptoms the prognosis is appreciably worse if at least one of the three is specific than if, in the presence of two symptoms, one is specific.

all in the premature. Convulsion as well as irritability were found on their own in a few mature children and were not invariably indicative of a poor prognosis. Cyanosis, which was the commonest single symptom, most often implied a favourable prognosis.

2 Patients with two or three non-specific symptoms

The later fate of infants showing two or three non-specific symptoms apparently did not differ from those who exhibited only one unspecific symptom (see Tables 25 and 26) The distribution within Groups I–IV in the latter group taken as a whole, was 7 17 21 and 55 per cent and in the former 5 25 25 and 45 respectively

3 Patients with one specific and one non-specific symptom

This combination was found in only a small number of cases. Table 27 gives the figures, from which it can be seen that the presence of one specific plus one non-specific symptom from a prognostic point of view equals the presence of non-specific symptoms only

TABLE 27

Relationship between neonatal symptoms and later condition in the presence of one specific plus one non specific symptom

Neonatal symptoms	BW > 2500 g 8 patients					BW < 2500 g 3 patients				
	Follow-up groups									
	No.	I	II	III	IV	No.	I	II	III	IV
Convulsion + cyanosis	3			2	1	1				1
Convulsion + flaccidity	1		1							
Tremor + cyanosis	2				2	1				1
Irritability + respir disorder	0					1			1	
Irritability + flaccidity	1	1				0				
Rigidity + cyanosis	1				1	0				
All patients in both weight groups	11	1	1	3	6					

4 Patients with two specific symptoms

This combination was seldom found in the mature and not at all in the premature (see Table 28) The figures do not allow any conclusion to be drawn but suggest a tendency towards a more unfavourable prognosis. three of the eight patients are found in Group I however the likelihood of a normal development exists.

These four groups comprise well over half the mature (75) and about two-thirds (20) of the premature infants surviving the neonatal period.

These figures apply to the mature patients.

The small size of the premature groups makes an evaluation very difficult; however, it should be noted that even in the presence of as many as three neonatal symptoms, where one or two are specific, this need not indicate an unfavourable prognosis for the premature.

The prognostic significance of various forms of cyanosis

Table 32 gives the relationship between later condition and cyanosis in its various forms, either occurring alone or in association with other symptoms.

Cyanosis occurring within the first few hours of life was found exclusively in association with other symptoms and was usually compatible with a good prognosis.

Permanent cyanosis was seen in only two patients surviving the neonatal period. In each case it subsided within the first 24 hours of life and was associated with other symptoms. One of the patients is found in Group I, the other in Group IV

The figures in Table 32 apparently do not allow prognostic differentiation between cases where cyanotic attacks subsided within the first 24 hours of life and those where they persisted for several days.

Among the 32 cases with cyanotic attacks persisting over the first few days, 19 patients had recurrent attacks over two to four days, while in the remaining 13 cases the duration was five days or more. Of these 13 cases four were placed in Group I and four in Group IV while of the first

TABLE 32

Relationship between later condition and various forms of cyanosis

Monosymptomatic cyanosis			Follow-up groups BW > 2500 g No.	I	II	III	IV	BW < 2500 No.	I	II	III	IV
Attacks	*from 1st day*	for 1 day	9	1		1	7	2				2
		> 1 day	3			1	2	1		1		
	only after 1st day	for 1 day	1				1	1			1	
		> 1 day	0					2	1	1		
Cyanosis plus other symptoms												
Within the first few hours			7	1		4	2	0				
Permanent	*within 1st day*		2	1			1	0				
Attacks	*from 1st day*	*for 1 day*	28	4	7	4	13	7		1	2	4
		> 1 day	4	3	3	6	12	4	1	1	1	1
	only after 1st day	*for 1 day*	4		2		2	3		1		2
		> 1 day	6	2	2		2	0				

TABLE 30

Relationship between neonatal symptoms and later condition in the presence of one specific plus one non-specific plus one or more other symptoms

Neonatal symptoms	BW > 2500 g No.	I	II	III	IV	BW < 2500 g No.	I	II	III	IV
	Follow-up groups									
Convulsion + cyanosis	16	7	3		6	2		1		1
Convulsion + respiratory abnormality	9	3	2		4					
Convulsion + flaccidity	9	4	1		4	1				1
Tremor + cyanosis	16	7	3	2	4	3		1	1	1
Tremor + respiratory abnormality	11	4	2	1	4	2			1	1
Tremor + flaccidity	11	6	2	1	[illegible]	1				1
Irritability + cyanosis	11	7	1	1	2	1		1		
Irritability + respiratory disorder	10	5	1		4					
Irritability + flaccidity	1[illegible]	8	1	1	2					
Rigidity + cyanosis	15	7	3		5					
Rigidity + respiratory abnormality	9	4	1		4	1	1			
Rigidity + flaccidity	10	7			3	1	1			
BW > 2500 g		40–60 %			20–40 %					

Table 31 shows the same relationship in the presence of at least three neonatal symptoms, where two are specific. The prognosis is usually poor with 60–80 per cent being placed in Group I and is worse than in the case of two specific symptoms occurring alone or in one specific together with two non-specific symptoms (see Tables 28 and 30)

TABLE 31

The relationship between neonatal symptoms and later condition in the presence of two specific plus one or more additional symptoms

Neonatal symptoms	BW > 2500 g No.	I	II	III	IV	BW < 2500 g No	I	II	III	IV
	Follow-up groups									
Convulsion + tremor	14	8	1		5	1		1		
Convulsion + irritability	13	11	1		1	1		1		
Convulsion + rigidity	14	9	2		3	0				
Tremor + irritability	14	10	2		2	1		1		
Tremor + rigidity	14	9	2		3	0				
Irritablity + rigidity	14	12	1		1	0				
BW > 2500 g		60–80 %			10–20 %					

The duration of the convulsions, whether of early or late onset, seems to offer a clue to the prognosis. Of seven children who had convulsions from the first day of life the two in Group I exhibited this symptom for respectively five days and beyond two months, the remaining for two or three days only In six of the seven children in Group I, who had delayed convulsions lasting for more than 24 hours, the symptom persisted for 3–5 days (in the 7th for 2 days) while all others had seizures for two or three days.

In the one patient in Group IV with late onset of convulsion as the only symptom, the symptom persisted for three days.

Cyanotic attacks developing after the first 24 hours of birth invariably began on the second or third day This was true in two-thirds of the infants who developed convulsions. In the remaining one-third, convulsions developed from one to three weeks after birth. There was no correlation between time of onset, and duration of the convulsions or the severity of sequelae.

Conclusion

Mature patients

A fairly good prognosis is likely in the presence of

1) one neonatal symptom, whether specific or non-specific, *or*
2) two symptoms, even though one is specific, *or*
3) three non-specific symptoms.

Severe cerebral sequelae have been found in less than 10 per cent of such cases, and a perfectly normal development was found in about 50 per cent—or 75 per cent if Group III with questionable sequelae is included.

4) The presence of two specific symptoms seems to imply a worse prognosis, with about 30 per cent risk of severe cerebral sequelae.
5) With a combination of no less than three symptoms, at least one of which is specific, the prognosis is poorer with a 40–60 per cent risk of severe cerebral sequelae.
6) At least three symptoms including two specific ones usually indicate a poor prognosis with a 60–80 per cent risk of severe cerebral sequelae.
7) Cyanotic attacks in association with other symptoms developing within the first day of life are found to be an unfavourable prognostic sign when persisting for more than four days. If cyanotic attacks begin later than the first day of life, a duration beyond only two days, seems to imply a poor prognosis.
8) Convulsion, which very rarely occurred on its own, seems to indicate a poor prognosis in a great proportion of cases, even if limited to 24 hours. However convulsion lasting for two or three days may be compatible with a good prognosis. If the duration exceeds three days, the outlook appears graver

mentioned 19 cases none were found in Group I and 10 in Group IV Of the four infants who had cyanotic attacks as the sole symptom during the first few days, only one (from Group IV) had attacks for as long as 5 days in the remaining cases the duration was 2 days only

As might be expected the time factor influenced the prognosis, though long duration of the symptoms was not always a bad sign.

Late onset of cyanosis, which in those dying within the neonatal period was seen only in association with cerebral haemorrhage or oedema, in the case of the survivors did not apparently indicate a worse prognosis than early cyanosis limited to the first 24 hours of life.

17 patients had delayed cyanotic attacks In the nine the attacks lasted for 24 hours, in eight for more than 24 hours (between 2 and 4 days, and in one case as long as 20 days) In most cases the onset was on the second or third day of life.

None of these 9 patients are to be found in Group I five are in Group IV Among the 8 cases three are in Group I two in Group IV Here, too, the importance of the time factor is apparent, while the outlook was grave with early cyanosis persisting for more than four days, this also seemed to be the case with delayed cyanosis lasting for only two days.

The prognostic significance of the time factor in convulsion

Table 33 shows the later course in those groups in which convulsion developed within the first 24 hours or later divided according to the duration of the seizures.

Allowing for the small numbers in each group it is concluded that convulsion in association with other symptoms, whether occurring early or late, and even when limited to 24 hours, almost certainly implies a poor prognosis.

TABLE 33

Time of onset and duration of neonatal convulsion in relation to later condition

Convulsion + other symptoms		BW > 2500 g					Follow-up groups BW < 2500 g				
		No.	I	II	III	IV	No.	I	II	III	IV
From 1 st day	for one day	9	4		2	3	0				
	> one day	7	2	2	2	1	0				
Only after 1 st day	for one day	4	1	1		2	3		1		2
	> one day	12	7	1		4	0				
Convulsion as sole symptom											
Only after 1 st day	for one day	1	1								
	> one day	1				1					

CHAPTER VI

Pre- and perinatal conditions

This chapter deals with conditions during pregnancy and delivery and the immediate postnatal state of the infant. These data are correlated with the neonatal symptoms and later development of the child with a view to assessing whether aetiological variations might influence the diagnostic and prognostic significance of the neonatal symptoms.

Complications of pregnancy

In 33 mothers, or 12 per cent of the cases, a total of 36 complications of pregnancy were reported, as listed in Table 34

TABLE 34

Complications of pregnancy in 33 patients

Toxaemia with hypertension	6
Oedema and albuminuria	4
Hyperemesis	7
Unspecified malaise	4
Vaginal bleeding	4
Hydramnios	4
Miscellaneous	7
Total	36

The hypertension in one of the toxaemic patients probably was nephrogenic: 10 years before delivery a right-sided hydronephrosis had been demonstrated, and an operation on the right ureter had been performed 4 years later The patient had suffered repeated urinary infections, on the last occasion 10 days before delivery Her systolic blood pressure purportedly had been 200. Of the other five cases two were mild and three were more severe. In one of these three there had also been vaginal bleeding during the third month of pregnancy

Premature patients

The evaluation is very difficult, firstly because very few of these infants survived the neonatal period secondly premature infants usually present very few symptoms, and obviously fewer specific symptoms than the mature. However it should be noted that the presence of as many as three symptoms, including one or two specific symptoms, is not tantamount to a poor prognosis.

TABLE 36

Complications of pregnancy and deli ery in 17 patients

Occurrence during pregnancy	Complications of	
	Pregnancy	Delivery
Early (4 patients)	Hyperemesis	Precipitate delivery
	Hyperemesis	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Gynaecologic surgery	Poor heart sound
Late (6 patients)	Toxaemia	Placenta praevia
	Toxaemia	Premature placental separation
	Toxaemia	Forceps delivery
	Toxaemia	Prolonged delivery
	Oedema, albuminuria	Prolonged delivery
	Jaundice m. VIII	Breech delivery
Throughout (7 patients)	Hyperemesis	Placenta praevia
	Hyperemesis	Prolonged delivery
	Hyperemesis	Prolonged delivery
	General malaise	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Anaemia	Precipitate delivery

The exact duration of the delivery was rarely stated, however a delivery has been classified as prolonged only if it is known to have lasted for more than 24 hours, and as precipitate if its duration was less than two hours.

The abnormal presentations were as follows: breech or breech-footling in seven cases, deep transverse in two cases, transverse in one and anterior vertex in four

In one case of premature placental separation there was also precipitate delivery and early rupture of membranes. In another such case there was breech presentation. In one case of primary inertia the presentation was anterior vertex, and in two the infant had the cord around the neck.

In 17 out of 33 cases with complications of pregnancy there were also delivery complications (see Table 36) The combinations were numerous. Abnormal deliveries were more frequent in those cases where complications had persisted throughout the pregnancy

In the much larger group of cases (242) with uncomplicated pregnancy the incidence of delivery complications was 43 per cent.

Asphyxia

As regards the condition of the infants immediately after birth the only reliable information concerns the presence or absence of asphyxia.

Asphyxia, as already mentioned, is defined here as delayed establishment

Four mothers had oedema and albuminuria in the presence of normal blood pressure. Two of these also had hyperemesis

A total of seven mothers had hyperemesis, three during the first half, four throughout the pregnancy

Vaginal bleeding occurred in four cases in three during the third month, the fourth had spot bleeding throughout the pregnancy

Four had hydramnios, the degree of which had not been stated. One was known to have developed acutely during the last weeks of pregnancy

"Miscellaneous" comprises three early and three late complications as well as one case of unspecified anaemia, which persisted throughout the pregnancy The early complications comprised two cases of minor gynaecological surgery during the first and second month (excision of a cyst of the corpus luteum and of a uterine polyp, respectively) The third mother had rubella during the third month.

The late complications were as follows. in two cases a febrile illness, presumably influenza, immediately before and during the delivery a third mother had jaundice, unassociated with fever or other symptoms, persisting for two weeks during the eighth month She had experienced similar conditions during previous pregnancies.

In all, 10 complications were limited to the first half of the pregnancy while 18 occurred in the latter half and eight persisted throughout.

Complications of delivery

In 121 or 44 per cent of the cases, 127 complications of delivery were reported (Table 35) The rate of complications in deliveries taking place outside the home in 1950 was 21 4 per cent in Copenhagen County Table 35 shows the findings

TABLE 35

Complications of delivery in 121 patients

		Prolonged delivery	Manual extraction	Forceps delivery	Caesarean section
Abnormal presentation	14	6	–	4	1
Cranio-pelvic disproportion	4		–		1
Prolonged, uncompl. delivery	48	48		15	–
Precipitate delivery	23	–	–	–	–
Primary inertia	7	5	1	2	–
Placenta praevia	3	–	–	–	2
Premature placental separation	4	–	1	–	–
Early rupture of membranes	7	2	–	–	–
Poor foetal heart sound	5	2	1	3	–
Cord around the neck	8	3	1	–	–
Normal (?) delivery	4	–	3	1	–
	127	68	9	27	4

TABLE 36

Complications of pregnancy and delivery in 17 patients

Occurrence during pregnancy	Complications of Pregnancy	Complications of Delivery
Early (4 patients)	Hyperemesis	Precipitate delivery
	Hyperemesis	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Gynaecologic surgery	Poor heart sound
Late (6 patients)	Toxaemia	Placenta praevia
	Toxaemia	Premature placental separation
	Toxaemia	Forceps delivery
	Toxaemia	Prolonged delivery
	Oedema, albuminuria	Prolonged delivery
	Jaundice m. VIII	Breech delivery
Throughout (7 patients)	Hyperemesis	Placenta praevia
	Hyperemesis	Prolonged delivery
	Hyperemesis	Prolonged delivery
	General malaise	Precipitate delivery
	Vaginal bleeding	Prolonged delivery
	Anaemia	Precipitate delivery

The exact duration of the delivery was rarely stated, however a delivery has been classified as prolonged only if it is known to have lasted for more than 24 hours, and as precipitate if its duration was less than two hours.

The abnormal presentations were as follows. breech or breech-footling in seven cases, deep transverse in two cases, transverse in one and anterior vertex in four

In one case of premature placental separation there was also precipitate delivery and early rupture of membranes. In another such case there was breech presentation. In one case of primary inertia the presentation was anterior vertex, and in two the infant had the cord around the neck.

In 17 out of 33 cases with complications of pregnancy there were also delivery complications (see Table 36) The combinations were numerous. Abnormal deliveries were more frequent in those cases where complications had persisted throughout the pregnancy

In the much larger group of cases (242) with uncomplicated pregnancy the incidence of delivery complications was 43 per cent.

Asphyxia

As regards the condition of the infants immediately after birth the only reliable information concerns the presence or absence of asphyxia.

Asphyxia, as already mentioned, is defined here as delayed establishment

Four mothers had oedema and albuminuria in the presence of normal blood pressure. Two of these also had hyperemesis.

A total of seven mothers had hyperemesis three during the first half, four throughout the pregnancy

Vaginal bleeding occurred in four cases in three during the third month the fourth had spot bleeding throughout the pregnancy

Four had hydramnios the degree of which had not been stated. One was *known to have developed acutely during* the last weeks of pregnancy

Miscellaneous comprises three early and three late complications as well as one case of unspecified anaemia, which persisted throughout the pregnancy The early complications comprised two cases of minor gynaecological surgery during the first and second month (excision of a cyst of the corpus luteum and of a uterine polyp respectively) The third mother had rubella during the third month.

The late complications were as follows In two cases a febrile illness, presumably influenza, immediately before and during the delivery a third mother had jaundice, unassociated with fever or other symptoms, persisting for two weeks during the eighth month She had experienced similar conditions during previous pregnancies

In all, 10 complications were limited to the first half of the pregnancy while 18 occurred in the latter half and eight persisted throughout.

Complications of delivery

In 121 or 44 per cent of the cases, 127 complications of delivery were reported (Table 35) The rate of complications in deliveries taking place outside the home in 1950 was 21 4 per cent in Copenhagen County Table 35 shows the findings

TABLE 35

Complications of delivery in 121 patients

		Prolonged delivery	Manual expulsion	Forceps delivery	Caesarean section
Abnormal presentation	14	6	–	4	1
Cranio-pelvic disproportion	4	2	–	2	1
Prolonged, uncompl delivery	48	48	2	15	–
Precipitate delivery	23	–	–	–	–
Primary inertia	7	5	1	2	–
Placenta praevia	3	–	–	–	2
Premature placental separation	4	–	1	–	–
Early rupture of membranes	7	2	–	–	–
Poor foetal heart sound	5	2	1	3	–
Cord around the neck	8	3	1	–	–
Normal (?) delivery	4	–	3	1	–
	127	68	9	27	4

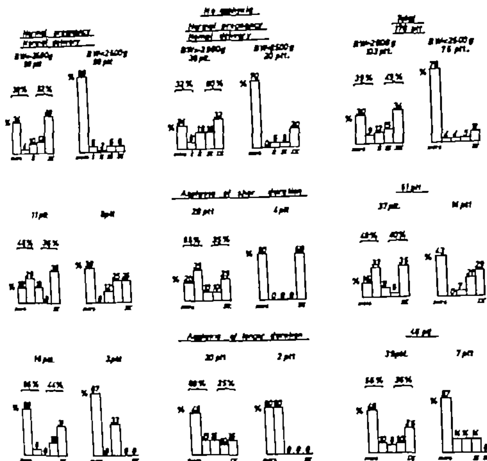


Fig. 9

Relationship between conditions during pregnancy and delivery occurrence of asphyxia and the later conditions of the children.

Mort: Patients dying during the neonatal period.
I. Patients with severe cerebral sequelae.
II. Patients with minor cerebral sequelae.
III: Patients with mild deviations of presumably cerebral origin.
IV: Patients with normal development.

hence only these two have been considered. (The other groups comprised 10 cases or less)

In the following section only mature infants are considered, since the question of prematurity will be dealt with in Chapter VII. The respective groups have been subdivided according to the presence and duration of primary asphyxia on the assumption that any factor which gives rise to

of spontaneous respiration after birth. It was observed in 97 children (35 per cent) These figures however represent an absolute minimum, since the administration of drugs immediately after birth in several additional cases indicated the presence of asphyxia, even though this had not been stated explicitly

These 97 cases have been divided into two groups according to the dura tion of the asphyxia, with an arbitrary line drawn at 5 minutes. In 51 the asphyxia was of short duration in 46 it was prolonged.

The combinations of the factors mentioned above are shown in Table 37 It will appear that in one-half (138) of the cases there were no complications of pregnancy or delivery or at least no recognized complications. About one-quarter of these exhibited asphyxia, which in half the cases was prolonged.

TABLE 37

Asphyxia related to conditions of pregnancy and birth

Normal pregnancy normal delivery 138 pat.	no asphyxia 100 pat. (72 %) + asphyxia 38 pat. (28 %)
Compl pregnancy normal delivery 16 pat.	no asphyxia 12 pat. (75 %) + asphyxia 4 pat. (25 %)
Normal pregnancy compl. delivery 104 pat.	no asphyxia 58 pat. (56 %) + asphyxia 46 pat. (44 %)
Compl. pregnancy compl. delivery 17 pat.	no asphyxia 8 pat. (47 %) + asphyxia 9 pat. (53 %)

In the small group with complicated pregnancy and normal birth the incidence of asphyxia, including that of long duration, was the same.

Complicated deliveries, as might be expected, were followed by a higher incidence of asphyxia, twice as high as normal deliveries. Again about half the patients had prolonged asphyxia, regardless of the conditions of pregnancy

The influence of pre and perinatal factors on prognosis and neonatal symptoms

The relationship between the course of pregnancy and delivery and the condition at follow up has been analysed separately in the following combinations. normal pregnancy–normal delivery complicated pregnancy–normal delivery normal pregnancy–complicated delivery abnormal pregnancy–abnormal delivery This subdivision gave a number of fairly small groups. Only the group with normal pregnancy and normal delivery and that with normal pregnancy and complicated delivery were of a fairly acceptable size,

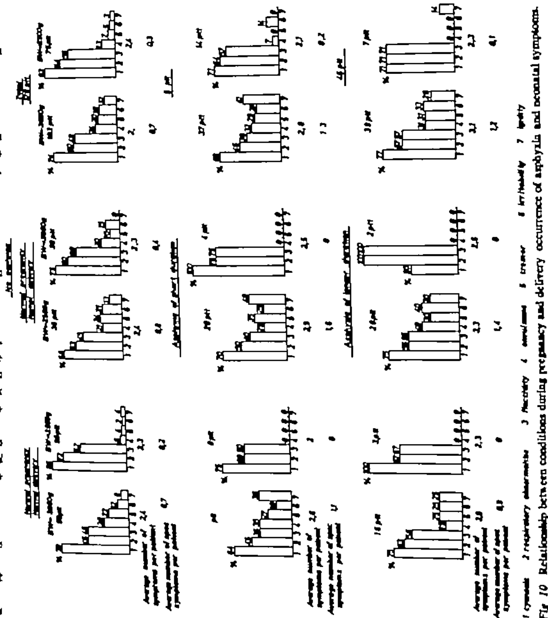


Fig 10 Relationship between conditions during pregnancy and delivery occurrence of asphyxia and neonatal symptoms.

groups—that even in the presence of few (less than three) neonatal symptoms following a normal birth a good prognosis must be made with caution, whereas optimism is more justified when a similar symptomatology follows a complicated birth.

asphyxia as well as neonatal symptoms will have a stronger influence than one that does not precipitate asphyxia. However the resulting groups are so *small* that the figures must be treated with reserve Therefore, analyses have also been made for the group as a whole in relation to the presence or absence of asphyxia, regardless of conditions during pregnancy and delivery

As may be seen from Fig. 9 the course of delivery apparently has no bearing on the prognosis, since the magnitude of the follow up groups is essentially equal whether the delivery was normal or complicated. In con trast, there are in each delivery group far more cases with severe sequelae following brief asphyxia than in the absence of asphyxia and there is a distinctly higher immediate mortality following prolonged asphyxia than in any other group This seems to support the validity of asphyxia as an indication of the severity of a given influence.

Fig. 10 similarly illustrates the relationships between delivery asphyxia and the incidence of neonatal symptoms. It will appear that brief asphyxia was associated on average with a greater number of symptoms per patient, viz. 2.6 and 2.9 after normal and complicated births, respectively compared with 2 4 in the cases without asphyxia. Moreover specific cerebral symptoms were more frequent following asphyxia. Prolonged asphyxia was followed by a further increase in the average number of symptoms, but some de crease in the frequency of specific symptoms, a relation which, as shown before (p 7) generally held good for the patients who died in contrast to those who survived, cf the high primary mortality following prolonged asphyxia.

The survivors similarly have been separately analysed and correlations were found to be parallel except for the highest incidence of specific cerebral symptoms being found in patients with prolonged asphyxia following a complicated delivery (average of 1 7 symptoms per patient)

The question is whether these variations in the incidence of symptoms may prove of practical prognostic value.

To take two extremes, Table 38 shows the average number of symptoms found in all the full term infants who later exhibited severe cerebral sequelae (Group I) and in all those who developed normally (Group IV) It is apparent that one main group, viz. that of all full-term children in Group I whose delivery had been complicated differs from the remainder in that it exhibits a greater number of symptoms (an average of 4 per cent) and also more specific symptoms per patient. However a matter of greater interest in this connection is those infants in Group I whose delivery was uncom plicated, in that their average number of symptoms is similar to that of the children in Group IV regardless of the course of delivery

It is evident—though allowance must be made for the small size of the

frequency following normal and complicated delivery. In infants whose brains were abnormal the average number of symptoms, including the specific ones was slightly higher following complicated than following normal delivery. But one can hardly attach practical importance to these differences.

Parity and maternal age at delivery

132 of the mothers—or 48 per cent—were primiparas. 18 were more than 30 years old, as were 34 of the 143 multiparas. The incidence of primiparity in Copenhagen in 1955 was 37 per cent (*Kærn* 1955).

The incidence of complications of pregnancy and delivery in the respective parity- and age-groups can be seen from Tables 40 and 41. In elderly multiparas the frequency of pregnancy complications was slightly higher than in the other groups; in elderly primiparas complicated deliveries were somewhat more frequent.

TABLE 40

Complications of pregnancy correlated with parity and maternal age

	Total no.	No. with compl.	Per cent with compl.
Primiparas < 30 years	114	12	11
Primiparas > 30 years	18	1	6
Multiparas < 30 years	109	12	11
Multiparas > 30 years	34	8	24

TABLE 41

Complications of delivery correlated with parity and maternal age

	Total no.	No. with compl.	Per cent with compl.
Primiparas < 30 years	114	52	46
Primiparas > 30 years	18	11	61
Multiparas < 30 years	109	43	39
Multiparas > 30 years	34	15	44

In children of younger mothers asphyxia was commoner following complicated than following normal births, but showed no evident relationship to parity (see Table 42). In children of elderly primiparas (small figures only) asphyxia was common regardless of the course of delivery. However, as in the case of younger mothers, it was more frequent following complicated than following normal birth, when the mother was an older multipara. Prolonged asphyxia was evenly distributed throughout the groups.

TABLE 38

A comparison between average number of neonatal symptoms in full-term patients developing severe cerebral sequelae (I) and children developing normally (IV), correlated with conditions during pregnancy and delivery and the presence or absence of asphyxia.

	No. pat. group		Average no. per patient of symptoms		specific symptoms	
	I	IV	I	IV	I	IV
Pregn. normal deliv normal − asphyxia	2	20	2.5	2.1	2.5	0.8
Pregn. normal, deliv normal + asphyxia	4	9	2.8	2.3	1.5	0.9
Pregn. complic. deliv normal − asphyxia	1	1	2.0	3 0	1 0	0.3
Pregn. complic., deliv normal + asphyxia	0	2	0	2.5	0	1.0
Pregn normal, deliv complic. − asphyxia	3	12	4.3	1.9	3.3	0.5
Pregn. normal, deliv complic. + asphyxia	10	8	4 0	2.0	2.5	0 8
Pregn. complic., deliv complic. − asphyxia	3	2	4 0	2.5	3 0	0
Pregn. complic., deliv complic. + asphyxia	2	4	4 0	2.2	3.5	0.5

TABLE 39

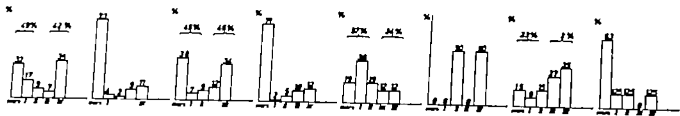
Autopsy findings in 122 infants who died in the neonatal period correlated with conditions during pregnancy and delivery

	No. pat.	Pregnancy: norm. Delivery: norm.	compl. norm.	norm. compl.	compl. compl.
Pulm. atelectasis, normal brain	20	15	1	4	0
Cerebral oedema, pulmonary atelectasis	19	17	0		0
Cerebral haemorrh. ± oedema, pulmonary atelectasis	61	28	6	26	1
Cerebral haemorrh. ± oedema, normal lungs	22	12	2	7	1
Total	122	72 (59 %)	9 (7 %)	39 (32 %)	2 (2 %)

Among the patients who died during the neonatal period more than half had a history of normal pregnancy and delivery (see Table 39) and well over half of these had intracranial haemorrhage. Following complicated deliveries by far the commonest cause of death was intracranial haemorrhage (85 per cent)

An analysis has been made of the incidence of symptoms in the patients with normal brains who died in the neonatal period following normal or complicated delivery and in patients with pathological brains following normal or complicated delivery

As already mentioned specific cerebral symptoms were absent in the former cases, and the three non-specific symptoms apparently occurred with equal



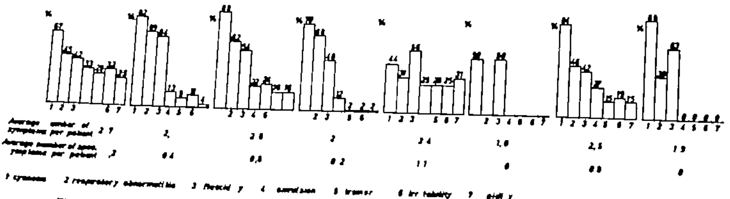


Fig 11 Relationship between maternal age and parity and a) The later condition of the children.
Morr Patients dying in the neonatal period.
I–IV Follow-up groups as described in Fig. 9 p. 87
b) Incidence of neonatal symptoms.

TABLE 42

Frequency of asphyxia in relation to maternal age and parity and course of delivery

Maternal age	Primiparas				Multiparas			
	No deliv compl.		+ deliv compl.		N deliv compl.		+ deliv compl.	
	− asph.	+ asph.	− asph.	+ asph.	− asph.	+ asph.	− asph.	+ asph.
< 30 years	42	20 (32 %)	29	23 (44 %)	50	16 (24 %)	24	19 (44 %)
> 30 years	4	3	6	5	16	3	7	8

In Fig. 11 maternal age and parity are correlated with the severity of late sequelae and the incidence of neonatal symptoms

The mortality rates were almost equal in full-term children of primi- and multiparas under 30 years (well over 30 per cent) and higher than in children of elderly mothers (well over 15 per cent)

The morbidity was higher among firstborn children and obviously the highest among children of elderly primiparas.

Among children of elderly primi- and multiparas mortality and morbidity were *essentially unrelated to the course of delivery*

Children of younger primiparas had a higher mortality (44 per cent) following a normal delivery than after a complicated delivery (24 per cent) whereas the morbidity was about the same.

Children of younger multiparas had a somewhat higher mortality rate (44 per cent) following a complicated than a normal delivery (37 per cent) *however severe sequelae were seen only* after complicated deliveries.

The symptomatology was unrelated to maternal age however firstborn children more often exhibited specific cerebral symptoms than children born to multiparas

Labour stimulating drugs

Information about the use of labour stimulating drugs is incomplete. On 123 out of 275 patients no data were available. In the remainder 35 deliveries are known to have been induced in 75 deliveries already in progress, labour stimulating drugs had been used and 42 had not been stimulated. In a great many cases where *stimulation had been applied, information on dosage* was inadequate.

Despite these deficiencies it was felt to be of interest to analyze the material with a view to detecting possible prognostic differences within the respective groups, particularly interesting because labour stimulation had been applied in 46 cases where no medical indication was stated. In 13 of these cases labour had been induced, in 33 it had been stimulated

Confronted with questions concerning the prognosis in individual patients it might be said that the prognosis is probably poor in the presence of many (more than three) symptoms including two or three of specifically cerebral origin, which is often the case following a complicated birth, regardless of the course of pregnancy or the presence of asphyxia. An infant born by normal delivery—irrespective of the course of pregnancy or presence of asphyxia—exhibiting two or three neonatal symptoms including one or two specific ones, may be prognostically as badly off (the fewer the specific symptoms, the better). If the same symptoms follow a *complicated delivery* the prognosis will more often be favourable.

The children of elderly primiparas showed no symptomatological differences from children of younger primiparas however their long-term prognosis was worse. In firstborn children the long-term prognosis, regardless of the mother's age, was more grave than that of children born to multiparas however they exhibited on average a somewhat higher number of specifically cerebral symptoms.

Complicated pregnancies were too rare to allow definite conclusions as to their influence on the neonatal symptomatology or the prognosis. It was apparent, though, that complications of pregnancy had no decisive influence on the incidence of delivery complications nor of asphyxia.

Intracranial haemorrhage was found to be a common cause of death in cases of normal pregnancy and delivery however far more frequent following complicated delivery

Previous studies on the prognostic significance of perinatal conditions

The influence of perinatal conditions on the long-term prognosis has been discussed in numerous papers and conclusions have differed.

Retrospective studies on patients with cerebral palsy have fairly consistently revealed a high incidence of delivery complications. Thus *Plum* (1956) reported complicated deliveries in 50 per cent of his 87 hemiplegics and 202 quadriplegics, but in only about 25 per cent of 91 paraplegics and 14 ataxics. *Barclay* (1956) correspondingly found 46 per cent in 144 patients with cerebral palsy and moreover there was a significantly higher incidence of asphyxia following abnormal than normal deliveries. *Skatvedt* (1958) found delivery complications in 44 per cent of 370 children with cerebral palsy Also *Drillien et al.* (1962) reported a rate of about 50 per cent in a material of full-term and premature diplegics, over 25 per cent and 33 per cent in comparable control series. *Robo.* (1962) found a percentage of 31 in 198 children with cerebral palsy over some 10 per cent in a large control series.

Table 42 a lists the cases where pregnancy and delivery were normal and labour stimulation is known to have been used. Table 42 b gives the corresponding figures in cases with complicated pregnancy or delivery It will be seen that in the latter the prognosis was essentially the same whether stimulation had been applied or not. This is in contrast to the uncomplicated cases, where the prognosis is obviously graver following induced labour and somewhat worse following stimulated delivery than with non-stimulated delivery

TABLE 42 a

Relationship between use and non-use of labour stimulation and later condition in 69 cases with normal pregnancy and delivery

	No. pat.	Neonatal deaths per cent	Follow-up group I	II	III	IV
			per cent			
Induced delivery	13	38	23	8	15	15
Stimulated delivery	33	24	3	12	15	46
Not stimulated	23	9	4	22	17	48

TABLE 42 b

Relationship between use and non-use of labour stimulation and later condition in 83 cases with complicated pregnancy and delivery

	No. pat.	Neonatal deaths per cent	Follow-up group I	II	III	IV
			per cent			
Induced delivery	22	23	27	0	18	32
Stimulated delivery	42	21	17	17	19	26
Not stimulated	19	26	16	16	5	37

Conclusion

The incidence of complicated deliveries in the present series was found to be twice as high as in a normal population. However in 50 per cent of the cases pregnancy and delivery had been perfectly normal, and approximately two-thirds of these had not presented primary asphyxia.

This latter group did not differ in neonatal symptomatology nor with any degree of certainty in prognosis, from the group of non-asphyxiated patients whose births had been complicated.

In each group the presence of primary asphyxia was found to be associated with a somewhat higher number of symptoms per patient. This excess was largely due to an increase in the number of specific cerebral symptoms. Correspondingly the long-term prognosis was worse following asphyxia of short duration. Prolonged asphyxia on the other hand was associated with a high neonatal mortality

Confronted with questions concerning the prognosis in individual patients it might be said that the prognosis is probably poor in the presence of many (more than three) symptoms including two or three of specifically cerebral origin, which is often the case following a complicated birth, regardless of the course of pregnancy or the presence of asphyxia. An infant born by normal delivery—irrespective of the course of pregnancy or presence of asphyxia—exhibiting two or three neonatal symptoms including one or two specific ones, may be prognostically as badly off (the fewer the specific symptoms, the better) If the same symptoms follow a complicated delivery the prognosis will more often be favourable.

The children of elderly primiparas showed no symptomatological differences from children of younger primiparas, however their long-term prognosis was worse. In firstborn children the long-term prognosis, regardless of the mother's age, was more grave than that of children born to multiparas, however they exhibited on average a somewhat higher number of specifically cerebral symptoms.

Complicated pregnancies were too rare to allow definite conclusions as to their influence on the neonatal symptomatology or the prognosis. It was apparent, though, that complications of pregnancy had no decisive influence on the incidence of delivery complications nor of asphyxia.

Intracranial haemorrhage was found to be a common cause of death in cases of normal pregnancy and delivery however far more frequent following complicated delivery

Previous studies on the prognostic significance of perinatal conditions

The influence of perinatal conditions on the long-term prognosis has been discussed in numerous papers and conclusions have differed.

Retrospective studies on patients with cerebral palsy have fairly consistently revealed a high incidence of delivery complications. Thus *Plum* (1956) reported complicated deliveries in 50 per cent of his 87 hemiplegics and 202 quadriplegics, but in only about 25 per cent of 91 paraplegics and 14 ataxics. *Barclay* (1956) correspondingly found 46 per cent in 144 patients with cerebral palsy and moreover there was a significantly higher incidence of asphyxia following abnormal than normal deliveries. *Skatvedt* (1958) found delivery complications in 44 per cent of 370 children with cerebral palsy Also *Drillien et al.* (1962) reported a rate of about 50 per cent in a material of full-term and premature diplegics, over 25 per cent and 33 per cent in comparable control series. *Roboz* (1962) found a percentage of 31 in 198 children with cerebral palsy over some 10 per cent in a large control series.

Opinions have differed on the role of delivery complications in the aetiology of cerebral palsy However it can hardly be doubted that a pathological delivery in certain cases is of primary significance. Several prospective studies have led to the opposite conclusion.

Wetterdal (1951) carried out a follow-up study at age 12 years, on 2000 children delivered spontaneously and 2000 children delivered by forceps, of whom about one-quarter had exhibited perinatal asphyxia. He found a higher neonatal mortality among the latter By contrast, there were no differences in the incidence of physical or mental handicaps 75 per cent were perfectly normal. The follow-up percentage was 82–85

Keith Norval and *Hunt* (1953) concluded that neither prolonged delivery nor asphyxia caused neurological abnormalities in children who survived the neonatal period. This conclusion was based on follow up examination at the age of 4 years of approximately 400 children whose birth had been prolonged, well over 200 children who had exhibited primary asphyxia, and controls for both groups. Their findings were confirmed at re-examination at the ages of 4 to 14 years (*Keith* and *Gage* 1960) The follow-up percentage was 76–79 All the groups included children who had exhibited neonatal symptoms a majority were found in the asphyxia group (23 per cent) almost as many in the groups with prolonged delivery (8 per cent) as in that with normal delivery (4 per cent) Among these infants the neonatal mortality was very high (about 50 per cent) regardless of the course of delivery or of asphyxia, but the children who survived the neonatal period were neurologically normal The mortality rate in the present material thus is somewhat lower while the late morbidity is much higher This may be ascribed to differences in selection. Keith and Norval's series came from an obstetric department and is apt to include more cases of neonatal deaths. The current material is composed of children who had survived the first few hours or days of life, however exhibited symptoms severe enough to prompt their transfer from the place of delivery to a paediatric department. At follow up those children from Keith and Norval's series who exhibited no neonatal symptoms but asphyxia were neurologically normal whereas in the groups with prolonged delivery and with normal delivery 4–5 per cent showed neurological deviations such as mental retardation, epilepsy febrile convulsion and squint. The defects were evenly distributed throughout the groups.

Benaron et al. (1953) correspondingly found similar prognoses in children surviving the neonatal period following prolonged labour plus forceps delivery even when associated with prolonged primary asphyxia, and following a normal delivery Precipitate deliveries, however were apt to leave residua. Each group consisted of well over 40 children, who were re-examined at the ages of 5–15 years.

Kremer and *Nack* (1957) carried out a follow-up study on 75 of 214 children delivered by forceps and 75 children born spontaneously and found no differences in mental development, nor did they find any neurological defects in any of the groups.

Primary asphyxia has been the subject of numerous studies. Its frequency is fairly consistent in unselected obstetric materials. *Russ, Strong* and *Christian* (1946) thus found rates of 2 to 3 per cent, *Campbell Cheeseman* and *Kilpatrick* (1950) had 4 4 per cent in well over 6000 births· *Benaron et al* (1960) 6 per cent in some 40 000 births, and *Hüter* (1962) 2.2 per cent in about 9 000 cases—all much lower than the incidence found in the present series (35 per cent)

As regards the influence of asphyxia on the later development of a child conclusions differ widely which to some extent may be explained by differences in the methods of selection as well as in the definition of asphyxia.

Several authors considered asphyxia as unimportant. *McPhail* and *Hall* (1941) collected precise data on the course of delivery and immediate postnatal condition in 1005 infants. 8.9 per cent had mild asphyxia (apnoea for less than one minute) 6 per cent had severe asphyxia (apnoea for more than one minute or cyanosis during the first few days of life) 0.7 per cent were stillborn, 1 1 per cent died during the neonatal period and 83.3 per cent had not exhibited asphyxia.—Mild asphyxia was found to be slightly commoner following prolonged deliveries. However a marked predominance of severe asphyxia was evident in cases with precipitate labour forceps deliveries and breech presentations. Mainly for geographical reasons only 270 children were re-examined at school-age. (The ratio of asphyxiated/non-asphyxiated cases was about the same as in the original series) No mental or behavioural differences were demonstrated in any group.

Similar findings were reported by *Campbell Cheeseman* and *Kilpatrick* (1950) on follow-up at ages 8–11½ years of children who had exhibited fairly severe asphyxia, viz. asphyxia pallida or asphyxia livida for more than two minutes. A greater number of asphyxiated than non-asphyxiated children had a history of complicated birth. The material consisted of 267 children, 178 of whom had not exhibited asphyxia. The follow-up rate was 73 per cent.

Usdin and *Weil* (1952) compared at the age of 13–14 years a group of full-term children who had exhibited neonatal asphyxia for more than three minutes, but were otherwise without cerebral features, with a matched control series. They found no difference in mental development between the two groups. The original material consisted of 180 patients, *but the follow-up* percentage was less than 50

Similarly *Ucko* (1965) found no difference in intellectual or emotional development between asphyxiated and non-asphyxiated children. On the

other hand, he found that the former were apt to exhibit marked sensitivity violent reactions and failure to adjust to new situations. Ucko's material consisted of 29 children who were neurologically normal, but had suffered varying degrees of asphyxia in the neonatal period, and 29 non-asphyxiated children. Their ages were up to five years at follow up

Other writers have found minor but still definite sequelae. *Fraser* and *Wilks* (1959) thus reported slight retardation of motor development and a possible perceptual disturbance (figure-background perception) but extensive investigations revealed no additional deviations. They had studied 100 asphyxiated children, of whom 40 had suffered severe asphyxia (i. e. for more than 5 minutes a majority for 15 minutes or more) All were born at term. Children who had presented cerebral symptoms in the neonatal period had not been excluded from the material Comparable controls were also examined. The age at follow up ranged from 7 to 11 years.

Walker (1964) found a tendency—though not of statistical significance—towards poorer performance, intellectually as well as physically in premature children who had suffered asphyxia neonatally compared with a group of non asphyxiated premature children and a group of non asphyxiated mature children. The age at follow up was 10 to 12 years. There were 41 children in each group

Stechler (1964) followed-up 26 full term firstborn children, of whom 9 had been asphyxiated for $2^1/_2$ to 16 minutes and found in the asphyxiated a significantly slower development up to the age of 2 years Thereafter their development was normal except for a somewhat more uneven performance between one test and the next.

Other writers found more definite correlation. *Darke* (1944) stated that 19 severely asphyxiated children showed significant mental retardation compared with a control series The criteria for selection were asphyxia pallida *or asphyxia exceeding three minutes in the absence of neurological symptoms* during the neonatal period as well as later

Benaron et al (1960) also reported a higher incidence of mental retardation (20 per cent) among 30 children who had sustained severe neonatal asphyxia persisting for not less than 10 minutes to more than an hour compared with 54 controls (2.5 per cent) The average IQ score, on the other hand, was equal in the two groups, indicating a greater spread among the asphyxiated. The latter moreover had a higher rate of EEG-abnormalities and persistence of infantile habits. There were, however no developmental or neurological differences. About 70 per cent of the children were re-examined at the age of 10 years.

Ernhart Graham and *Thurston* (1958) and *Graham Ernhart* and *Thurston* (1962) found that children who had sustained perinatal anoxia, particularly post-natal, often showed a poor intellectual performance and also ex

hibited more neurological defects at the age of three years than children who were neonatally normal. The series consisted of 116 full-term anoxic children, of whom 36 had showed evidence of possible intrauterine anoxia, 42 of postnatal anoxia of varying degree (apnoea persisting for less than one minute to over 4 minutes or secondary apnoea only) and 38 of prenatal as well as postnatal anoxia. None had exhibited other cerebral features. The control series consisted of 159 mature children. The follow-up rate was about 85 per cent.

In another investigation *Graham, Ernhart, Thurston* and *Craft* (1962) studied a small group of children who had presented clinical evidence of birth injury during the neonatal period. At the age of three years they differed from a normal group only in terms of a significantly higher incidence of neurological defects.

Hüter (1962) over a three-year period gathered 201 full-term infants exhibiting asphyxia of varying degree (apnoea ranging from less than one minute to over four minutes, associated with varying changes of muscle tone) 27 children, who had been severely asphyxiated, died within the neonatal period, their neonatal condition, however, was not described. 104 (about 50 per cent) were re-examined at the age of 2 to 6 years. The incidence of sequelae was very high. 27 per cent had cerebral palsy of varying degree, well over one half were also mentally retarded, as were 21 per cent who were neurologically normal. A positive correlation between the degree of cerebral damage and that of asphyxia was demonstrated. Similarly a positive correlation was established between the degree of asphyxia and conditions during pregnancy and delivery predisposing to hypoxia, however information about these conditions was only available in the cases exhibiting sequelae.

No clearcut conclusion can be drawn from this diversified picture. Conditions surrounding delivery are so complex that this could hardly be expected. The course of the delivery is not all-important; however it seems to be universally agreed that complicated deliveries are more often associated with asphyxia, and this is also demonstrated in the present material.

In most cases *Dekaban*'s statement (1959) will probably be true: the prognosis for life is grave in the presence of asphyxia pallida, though not in the milder forms of asphyxia. On the other hand, these are more often associated with late cerebral defects. The very mild forms apparently have no bearing on the later course. Yet even very prolonged asphyxia is compatible with later normal development. The uncertainty in establishing the prognosis is probably due to the difficulties in determining the origin of asphyxia, which may also play a decisive role. Neonatal symptoms seem to offer a more reliable prognostic indication than either the course of delivery or asphyxia.

CHAPTER VII

Prematurity

As previously mentioned 35 per cent of the children in the present material were premature (The prematurity rate in Copenhagen in 1948 was 7 per cent) For practical reasons the premature patients have been treated so far as one group which obviously is incorrect. In Table 43 the group has been subdivided according to BW and compared with the mature children.

As might be expected the mortality rate is higher the lower the BW Only two patients in the weight group of 1500–1000 grams survived the neonatal period. The one infant weighing less than 1000 gm died.

Otherwise it should be noted that the later progress of the premature survivors was as good as, if not better than the mature.

The premature infants, as previously stressed, exhibited on average fewer symptoms than the mature. This appeared to be more pronounced as the BW decreased. The number of symptoms per patient among premature survivors was, in the order of decreasing BW 2, 1 2, 1 and among those who died within the neonatal period. 2 9 2.5 2 1 and 2.

It should be noted, too that the rate of prematurity varied with maternal age. in mothers under 30 years it was 39 per cent among primiparas and 38 per cent among multiparas, while the corresponding rates in older mothers were 11 and 24 per cent, respectively

TABLE 43

Relationship of BW to mortality and results at follow-up

Birth weight in grams	No.	Neonatal deaths no.	Mortality rate per cent	No. of survivors	Follow-up group per cent I	II	III	IV
> 2500	179	55	31	124	20	15	18	47
2000–2500	39	21	53	18	11	17	17	55
1500–2000	35	26	74	9	22	–	56	22
1000–1500	21	19	90		–	100	–	–
< 1000	1	1	100	0				
< 2500	96	67	70	29	14	17	28	41

Complications of pregnancy were slightly more common prior to premature deliveries (13 per cent) than prior to deliveries at term (9 per cent) while complications of delivery were commoner at term (50 per cent) than before term (32 per cent)

Previous studies on the prognosis in premature infants

In view of the great difficulties of neonatal diagnostics in premature infants it was considered of special interest to compare the present study with a selection of the numerous investigations into the later progress of premature children. The following section includes only prospective studies. It may be mentioned, however that the prematurity rate in retrospective analyses of patients with cerebral palsy has been found to be uniformly high, ranging from 17 to 39 per cent (A. o. *Asher* and *Schonell* 1950 *Denhoff* and *Holden* 1951 *Barclay* 1956 *Plum* 1956, *Fuldner* 1957 and *Skatvedt* 1958)

But a few of the studies are immediately comparable. Some originate in obstetric clinics, others in paediatric departments. Consequently there may be differences in the composition of the materials due to differences in criteria for admission. Moreover the percentage of complicated deliveries varies at different obstetric clinics. Some series are unselected, others exclude patients with neonatal complications still others disregard patients without neonatal complications. Some include twins. Some apply a social selection. Moreover the upper limit of birth weights varies. some writers have included all infants below 2500 grams, while others incorporate only infants weighing less than 2000 or 1500 grams. Finally the follow-up rates vary considerably

Table 44 gives a survey of the results of previous studies, but considers severe sequelae only

It is apparent that the frequency of handicaps generally is higher amongst infants with a lower BW (cerebral palsy in 0.4–8.3 per cent with BWs up to 2500 gm, and 7–40 per cent below 1500 gm, the total incidence of severe handicaps being 5–20 per cent and 7–53 per cent, respectively)

This relationship has been particularly stressed by *Ylppö* (1919) and *Knobloch, Rider Harper* and *Pasamanick* (1956) Moreover several authors have found the average IQ of premature children to be obviously lower than in a comparable group of mature children (see among others *Ylppö* 1919 *Sunde* 1930 *Alm* 1953 *Blegen* 1953 *Drillen* 1959 and 1961 *Dann* 1958 and 1964 *Frisk* 1964 *Marstrander* 1964 and *Wohlmuth* and *Frater* 1965) Likewise the growth rate of the premature has been described as retarded by almost all workers, at least during the first years of life, and particularly in small prematures (all the authors mentioned above plus *Illingworth* 1939 and *Lubchenco et al.* 1963)

TAB[illegible]

Survey of previous studies [illegible]

Author	Year	Number	BW	Selection	Neonatal mortality %
Ylppö	1919				
Comberg	1927	233	≤ 2500 g	high soc. (pæd.)	58 (1 ye[illegible]
Capper	1928	437	≤ 2000 g	0 (pæd.)	44 (1 ye[illegible]
Sundø	1930	1423	≤ 2500 g	0 (ob.)	36 (1 ye[illegible]
Friedländer	1934	178	≤ 2500 g	0 (pæd.)	37 (1 ye[illegible]
Illingworth	1939	150	≤ 2500 g	0 (pæd.)	
Benlow	1949	289	≤ 2500 g	incl. 6 % neonatal sympt. (pæd.)	
Blegen	1953	1127	≤ 2500 g	0 (ob.)	13.5
Knobloch et al.	1956	500	< 2500 g	pæd. − gemelli	
		492	> 2500 g		
Harper et al.	1959	460	< 2500 g	pæd. − gemelli	
		440	> 2500 g		
Drillien	1959	165	< 2500 g	0 (pæd.)	
		427	> 2500 g	0 (pæd.)	
Frisk et al	1964	94	≤ 1750 g	0 (pæd.)	32
Heimer et al.	1964	444	≤ 2100 g	− gemelli, − cong. anomaly − bloodtype incompat. (pæd.)	
Mc Donald	1963	1128	≤ 1800 g	0 (pæd.)	
Marstrander	1964	80	< 2000 g (71 < 1500 g)	0 (pæd.) 14 abn. neonatal	−
Hess et al.	1934	69	≤ 2500 g	all sympt. neonatal (pæd.)	
Hess	1953	88	< 1250 g	all sympt. neonatal (pæd.)	
	−	1593	< 1250 g	pæd.	72
Drillien	1959	92	< 1360 g	0 (pæd.)	−
	1961	50	< 1360 g	0 (pæd.)	
Dann et al	1958	116	< 1280 g	0 (pæd.)	
Roesler	1962	175	< 1500 g	0 (pæd.)	
Lubchenco et al.	1963	187	< 1500 g	0 (pæd.)	47
Silagy et al.	1965	112	≤ 2500 g	susp. i. c. h. neonatal	
Wohlmuth et al.	1965	284	≤ 2500 g	0 (pæd.))	22

) 47 % of total material and 57 % of followed-up patients suspected of icr. haem. neonatally

H

...he prognosis of premature children

Follow-up rate of surveyed %	Age at follow-up years	Major sequelae	Total seq.
		3.1 % c. p. + 7 4 % mental defic.	10.5 %
83	3–7	2 % c. p., 3 % mental defic.	5 %
54	14	5 % c. p. + 7 % ment. defic. + 5 % epilepsy	17 %
62	6–21	7 % defic., incl. 5 7 % mental defic.	7 %
68	5–10	0 c. p., 19 % varying degree, mental defic.	19 %
	pre-school + schoolage	20 % c. p. + mental defic. + epilepsy	20 %
90	9–13	3 1 % c. p., 2.4 % debil. ment.	5.5 %
79	10–18	0.4 % c. p., 4.6 % mental defic., 7.5 % debil. ment.	12.5 %
91	40 weeks	BW ≤ 1500: 26 % neurol., 11.6 % mental defic.	38 %
		all BWs < 2500: 8.3 % neurol., 1.9 % mental defic.	10 %
		BW > 2500: 1.6 % neurol., 1.2 % mental defic.	2.8 %
77	3–5	BW ≤ 1500: 20.4 % neurol. handicaps	
		all BWs < 2500: 4.1 % neurol. handicaps	
		BW > 2500: 2.3 % neurol. handicaps	
	2	3 % c. p.	
	2	0.5 % c. p.	
54	6–7	40 % c. p.	
71		19 7 % neurol. abn.	19 7 %
96	6–8	6.5 % c. p.	
100	18 mo.		22 %
		40 % c. p., mental defic.	40 %
		33 % c. p., 13 7 % mental defic.	46 %
83	1 28	15 % phys. handicap, 11 % mental defic.	
	2 10	22 % neurol. handicaps, 14 % mental defic.	27 %
	aver. 5	12 % c. p., total 53 % phys. handic., 50 % ineducable norm. schools	
63	born 1940–52 exam. 1950–57	6.8 % c. p., epil., hearing loss	6.8 %
91	4–7	7 % c. p., 11.5 % mental defic.	
63	10	35 % c. p., 25 % mental defic.	
80	1 7	26 % mental defic. ± c. p. ± epil.	26 %
68	6–7	3 % c. p. + 3 % sensory defect + 47 % minor motor + mental	53 %

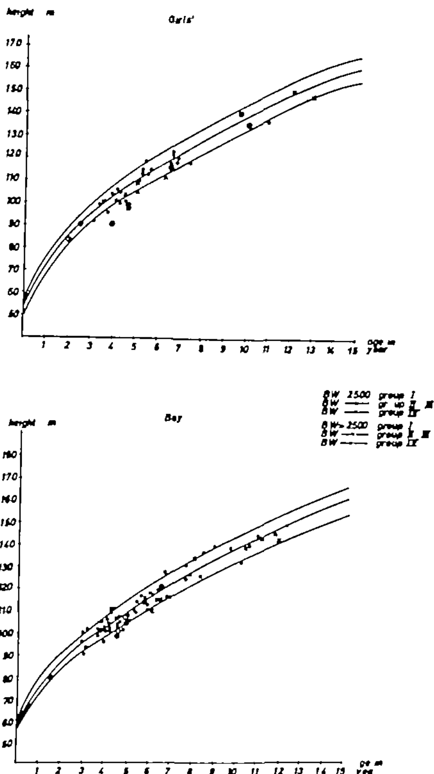


Fig 12

Height in centimetres at follow-up of 85 girls and 45 boys.
(Normal records according to A. Sundal, Nord. Lærebog i Pædiatri 1967).

Numerous hypotheses have been suggested as to the causes of these handicaps, a subject which, however is not under discussion in this book. It may be mentioned though that among others *Ylppö* (1919) *Comberg* (1927) *Hess* (1934), *Beskow* (1949), *Alm* (1953) and *Wohlmuth* and *Frater* (1965) advocate the theory of intracranial injury rather than prematurity itself as the causative factor This theory is supported by the fact that in the series dealing exclusively with premature children with neonatal symptoms suggesting intracranial damage there is a conspicuously higher incidence of sequelae (26–53 per cent) than in unselected materials. This is demonstrated among others by *Hess* (1934) *Beskow* (1949) *Silagy* (1965) *Wohlmuth* and *Frater* (1965) and also by the present author (31 per cent in Groups I and II)

In the small premature, however the rate of handicap is equally high whether the material is unselected or not. This may be explained by the fact that a large number of cases of cerebral damage in this weight group are almost entirely asymptomatic. This is at variance with *Drillien* (1959) who reported more neonatal cerebral symptoms in the weight group below 1500 grams than in a mature group. Nonetheless, the incidence of handicaps among the small premature remained unchanged regardless of the neonatal course.

The height has been measured in 130 of the 153 patients in the present series (26 premature and 104 mature) A total of 27 patients measured below lower normal borderline limits (see Fig. 12) Of these 7 were premature and 20 were mature, i. e. the premature (about one-quarter) outnumber the mature (about one-fifth) to only a small degree. It must be considered, though, that only two infants in the premature group had BWs below 1500 grams (both were of normal height) On the other hand there is a proportionally greater difference in the incidence of low height between Group I (8 out of 18) and the other groups (19 out of 112, evenly distributed in groups II, III and IV) This suggests that cerebral damage rather than prematurity in itself determines this aspect also

CHAPTER VIII

Sex differences

In the total material boys (63 per cent) outnumbered girls (the ratio between boys and girls born alive during the same period was approximately 52 over 48 per cent) As shown in Table 45 no prognostic differences between the sexes were demonstrable.

The rate of prematurity was somewhat higher in the girls (40 per cent) than in the boys (32 per cent) but mortality rate and long-term prognosis were equal within all weight groups.

One difference was found in the infants who died during the neonatal period. there was a significantly higher incidence of cerebral oedema in the boys (see Table 46) No explanation can be offered for this finding. As previously mentioned, the original series had been enlarged by 41 patients who died of cerebral oedema during the neonatal period Also in this group there was a predominance of boys over girls (27 and 14 respectively)

TABLE 45

Mortality and prognosis related to sex

	Neonatal mortality per cent	No. of survivors	Follow-up group I	II	III	IV
			per cent			
Girls 103 (37 per cent)	43	59	19	10	20	51
Boys 172 (63 per cent)	45	94	19	19	19	43

TABLE 46

Autopsy findings in 122 neonatal deaths related to sex

Autopsy findings	44 girls	78 boys
Pulmonary atelectasis, normal brain	10 (23 %)	10 (13 %)
Pulmonary atelectasis, cerebral oedema	2 (4 %)	17 (22 %)
Pulmonary atelectasis, cerebral haemorrhage ± oedema	24 (55 %)	37 (47 %)
Cerebral haemorrhage ± oedema, normal lungs	8 (18 %)	14 (18 %)
All patients with cerebral oedema	11 (25 %)	36 (46 %)

Summary

The object of the present study was the evaluation of the specificity of presumed cerebral symptoms and the prognostic value of neonatal symptoms.

Chapter I presents a review of previous literature on cerebral symptoms in newborn infants with special regard to studies comparing clinical and pathological findings. It is stressed that the clinical diagnosis of cerebral damage in the newborn is difficult, since the presenting symptoms are often non-specific and in many cases few in number. The commonest symptoms were cyanosis, respiratory irregularities, changes in consciousness and tone, convulsion and failure to suck. None of these, however, have been found to be specifically cerebral.

In addition, previous studies on the prognosis of intracranial neonatal disorders are reviewed. The materials are difficult to compare, primarily due to differences in the criteria of selection, but also because of great variations in the follow-up rates and in the age of the children at follow-up. In spite of these dissimilarities the incidence of severe cerebral sequelae varied as little as 10 to 30 per cent. However, opinions differ considerably as to what clinical symptoms may be of the greatest prognostic significance. No definite conclusion was possible.

Finally mention is made of some recent methods of investigation stressing the importance of the neurological examination during the neonatal period. The prognostic value of these studies can be judged only when long-term examinations have been completed.

Chapter II describes the present material, which includes 291 children who had been admitted to the Department of Paediatrics at Copenhagen County Hospital at Gentofte during the neonatal period. The data were obtained from the records, which had been selected on the basis of diagnoses that either 1) suggested cerebral damage: intracranial haemorrhage, sequelae of difficult delivery, fracture of the skull, asphyxia neonatorum, or 2) suggested the presence of some of the symptoms exhibited by the former group, such as pulmonary atelectasis, aspiration into the lungs, congenital debility. Patients who might have presented similar symptoms, but were re-

gistered under other definite diagnoses such as proven heart disease or hiatus hernia have been disregarded Patients with severe neonatal jaundice were also excluded In addition to neonatal symptoms and clinical course during admission all available information on pregnancy and delivery was recorded.

Most frequent among the neonatal symptoms was cyanosis, which occurred in three-quarters of the patients. Respiratory disturbances and flaccidity were observed in well over one half, convulsions in almost one-quarter and tremor irritability and rigidity in about one-fifth of the cases. A wide variety of combinations of these symptoms was recorded The average number of symptoms per patient was 2.5 Among the premature patients, representing 35 per cent of the series, the rate was somewhat lower (2.3) than among the mature (2 7) Convulsion, tremor irritability and rigidity were relatively rarer in the premature.

The patients were born in the period from 1946 to 1955 inclusive. The follow up examinations were performed from 1958 to 1959 Sixteen children had to be excluded owing to lack of information about their later development. Twelve had died after discharge from the hospital, but are nevertheless included in the material, since sufficient data on the subsequent course, in some instances detailed autopsy reports, were available. In six cases information derived only from written reports from the parents and/or their private doctor The remainder have been examined by the author The follow up rate is 95 per cent.

The follow-up included a general physical and neurological examination as well as an evaluation of the mental condition of the children. A meticulous history was taken, with special weight being given to mental, motor and somatic development. Moreover reports were obtained from specialists who, in some cases, had been consulted prior to the follow-up (psychological testing, eye and ear examinations, speech evaluation and electroencephalography) In a few instances, where it was thought to be indicated, and when practically possible, the children had been referred for such examinations in the course of the follow-up

In the description of *the results at follow-up* the cases have been divided into those dying during the neonatal period and four groups of survivors.

122, or 44 per cent of the patients died during the neonatal period. Macroscopic autopsy reports were available in all these cases, and the assessed causes of death as well as additional abnormal findings are described. In 84 per cent the primary cause of death was intracranial haemorrhage or cerebral oedema, or a combination thereof In 16 per cent there were no abnormal changes in the brain the cause of death being pulmonary atelectasis.

29 or 11 per cent (or 19 per cent of the survivors) had severe cerebral sequelae. 18 patients were mentally defective and exhibited severe neurolog-

ical symptoms, 7 had mental and motor handicaps of varying degree and 4 showed neurological symptoms, but had normal intelligence. 12 of the mentally retarded patients had died, the majority at the age of 2 to 3 years. Convulsion occurred in 16 speech retardation in 21 impaired hearing in at least 5 and squint in 15 patients. A description is given of EEGs in 21 cases, of pneumoencephalograms in 13 of brain sections in 7 and of head circumference in 20 Evidence of cerebral atrophy was found in 21 of these 29 patients.

24, or 9 per cent (or 16 per cent of the patients who survived the neonatal period) had minor cerebral sequelae in the form of mild mental retardation, temporary retardation of motor development or growth, recurrent convulsions—febrile or afebrile—hearing defects, aphasia or retardation of speech, temporary hyperactivity during the first one or two years of life, behaviour disorder squint and enuresis. All the children exhibited more than one of these features in varying combinations. None had permanent motor handicap.

30, or 11 per cent (or 19 per cent of the survivors) had mild, presumably cerebral deviations of similar kind, however less pronounced than in the previous group, and most of the children exhibited a single symptom only In this group there were also five cases of dyslexia, but none of mental retardation, afebrile convulsion or hearing loss.

70, or 25 per cent (or 46 per cent of the survivors) presented no abnormal features.

The possible relationship between the abnormalities found at follow-up and the neonatal condition is discussed with reference to the literature. Adequate support is felt to have been forthcoming as far as later severe cerebral sequelae are concerned, but also for the milder symptoms, to maintain the assumption of a neonatal origin with reasonable certainty

In *Chapter III* the diagnostic significance of the neonatal symptoms is evaluated by comparing the features observed in patients dying during the neonatal period from 1) pulmonary atelectasis (associated with normal brain) (20 patients) 2) pulmonary atelectasis and cerebral oedema (19 patients) 3) pulmonary atelectasis and intracranial haemorrhage ± cerebral oedema (61 patients) and 4) intracranial haemorrhage ± cerebral oedema (normal lungs) (22 patients)

The symptoms of convulsion, tremor irritability and rigidity were found exclusively in patients with pathological brains. With a view to corroborating this observation the material has been expanded to include an additional 26 patients dying during the neonatal period of pulmonary atelectasis. None of these exhibited any of the aforesaid symptoms.

Although these symptoms thus seemed to be specifically cerebral, their absence by no means excludes the diagnosis of intracranial haemorrhage

gistered under other definite diagnoses such as proven heart disease or hiatus hernia, have been disregarded Patients with severe neonatal jaundice were also excluded In addition to neonatal symptoms and clinical course during admission all available information on pregnancy and delivery was recorded

Most frequent among the neonatal symptoms was cyanosis, which occurred in three-quarters of the patients. Respiratory disturbances and flaccidity were observed in well over one half convulsions in almost one-quarter and tremor irritability and rigidity in about one-fifth of the cases. A wide variety of combinations of these symptoms was recorded. The average number of symptoms per patient was 2 5 Among the premature patients, representing 35 per cent of the series, the rate was somewhat lower (2 3) than among the mature (2 7) Convulsion tremor irritability and rigidity were relatively rarer in the premature.

The patients were born in the period from 1946 to 1955 inclusive. The follow-up examinations were performed from 1958 to 1959 Sixteen children had to be excluded owing to lack of information about their later development. Twelve had died after discharge from the hospital but are nevertheless included in the material, since sufficient data on the subsequent course, in some instances detailed autopsy reports, were available. In six cases information derived only from written reports from the parents and/or their private doctor The remainder have been examined by the author The follow up rate is 95 per cent.

The follow up included a general physical and neurological examination as well as an evaluation of the mental condition of the children. A meticulous history was taken, with special weight being given to mental, motor and somatic development. Moreover reports were obtained from specialists who, in some cases, had been consulted prior to the follow-up (psychological testing, eye and ear examinations, speech evaluation and electroencephalography) In a few instances, where it was thought to be indicated, and when practically possible, the children had been referred for such examinations in the course of the follow-up

In the description of *the results at follow-up* the cases have been divided into those dying during the neonatal period and four groups of survivors.

122, or 44 per cent of the patients died during the neonatal period. Macroscopic autopsy reports were available in all these cases, and the assessed causes of death as well as additional abnormal findings are described. In 84 per cent the primary cause of death was intracranial haemorrhage or cerebral oedema, or a combination thereof In 16 per cent there were no abnormal changes in the brain, the cause of death being pulmonary atelectasis.

29 or 11 per cent (or 19 per cent of the survivors) had severe cerebral sequelae. *18 patients were mentally defective and exhibited severe neurolog*

In the premature patients convulsion, as mentioned above, implied a graver prognosis. The other three specific symptoms occurred so rarely in the premature that their prognostic value cannot be estimated.

In *Chapter V* the neonatal symptoms are evaluated in relation to the long-term prognosis by comparing their incidence in the four follow-up groups of survivors (I. 29 patients with severe cerebral sequelae, II. 24 patients with minor cerebral sequelae, III. 30 patients with mild, presumably cerebral deviations, and IV 70 children with no abnormal findings at follow-up)

The average number of symptoms per patient is found, in the mature, to be the highest in Group I (3.6 over 2.1 in Group IV) Moreover there was a clear predominance of specific symptoms in Group I with 92 per cent having one or more such features over about 40 per cent of the mature children in the remaining groups and about 25 per cent among the premature in all groups.

An evaluation of the prognostic significance of each symptom and combination of symptoms in the full-term infants gave the following results. In the presence of a single *symptom*—whether specific or non-specific—the prognosis was relatively good, with a less than 10 per cent risk of severe cerebral sequelae and a 50 per cent chance of a perfectly normal development (75 per cent, if including Group III with dubious sequelae) The rates were essentially similar in the presence of two neonatal symptoms, even including one specific, and in the presence of three non-specific symptoms. When two specific symptoms were combined, the outlook appeared to be worse, with about a 30 per cent risk of severe cerebral sequelae. With an increasing number of symptoms, especially specific symptoms, the prognosis worsened. With a combination of not less than three symptoms, at least one being specific, there was a 40–60 per cent risk of severe sequelae and as high as 60–80 per cent, if no less than two of the symptoms were specific.

Cyanotic attacks—in association with other symptoms—when beginning during the first day of life and persisting beyond the fourth day were a grave prognostic sign. Delayed cyanotic attacks were prognostically unfavourable if persisting for more than 2 days, while attacks limited to one day had no serious implications.

Convulsions appeared to imply a fairly grave outlook, even when limited to one or two days, more so when persisting for more than three days.

In the premature the evaluation was somewhat difficult because so few patients survived the neonatal period, and partly because the premature mostly exhibited very few symptoms, in particular very few specific symptoms It was found, however that as many as three symptoms, even when one or two were specific, did not always imply a grave prognosis.

The role of aetiological factors as related to the diagnostic and prognostic

or cerebral oedema. 46 per cent of the mature infants and as many as 79 per cent of the premature whose brains were found to be abnormal at autopsy exhibited only cyanosis, respiratory abnormalities or flaccidity i.e. the features observed in patients who died from pulmonary atelectasis. The differential diagnosis between these groups is thus very difficult.

Permanent cyanosis was somewhat commoner among the infants with *pulmonary atelectasis on its own* while cyanotic attacks were more frequent among those with abnormal brain however both forms of cyanosis were too common in each group to allow diagnostic conclusions. In contrast, delayed cyanotic attacks (onset on the second or third day of life) were noted in brain-damaged infants only

The study revealed no clinical differences between cases of cerebral oedema and of intracranial haemorrhage. All the symptoms occurred with equal frequency in each group Neither was there any difference in the incidence of permanent or attackwise cyanosis nor in the time of onset of cyanosis. This also applied to time of onset and duration of convulsions.

The addition to the material of 41 patients dying of cerebral oedema during the neonatal period did not change these observations.

The significance of the neonatal symptoms for the prognosis for immediate survival is discussed in *Chapter IV* The infants who died during the neonatal period exhibited on average more symptoms than those who survived, and it is inferred that with an increased number of symptoms the risk for life is greater This was true in the mature patients, among whom the average number of symptoms was 3 1 against 2 5 in the survivors, as well as in the premature, where the corresponding figures were 2.5 and 1 7 However death did occur in the neonatal period, in a number of patients, mature as well as premature, who exhibited a single symptom only

The mortality rate has been calculated for each neonatal symptom occurring alone (which was rare) as well as in association with other symptoms. Cyanotic attacks within the first 24 hours of life, difficult and grunting respiration, hypotonicity and convulsion were found to imply a grave prognosis in the premature, the mortality rate being about 80 per cent, while in the mature it was only about 40 per cent. In mature infants cyanotic attacks beginning later than the first day were found to be a more unfavourable prognostic sign than cyanotic attacks occurring during the first day (mortality rate 56 against 27 per cent) Cyanotic attacks were commoner than permanent cyanosis (77 per cent over 23) The latter when persisting beyond a few hours, as in periodic apnoea, were invariably fatal as might be expected.

The more specifically cerebral symptoms convulsion, tremor irritability and rigidity seemed to indicate a less serious immediate prognosis in the mature (mortality rate 20–30 per cent) than the non specific symptoms.

In the premature patients convulsion, as mentioned above, implied a graver prognosis. The other three specific symptoms occurred so rarely in the premature that their prognostic value cannot be estimated.

In *Chapter V* the neonatal symptoms are evaluated in relation to the long-term prognosis by comparing their incidence in the four follow-up groups of survivors (I. 29 patients with severe cerebral sequelae, II. 24 patients with minor cerebral sequelae, III. 30 patients with mild, presumably cerebral deviations, and IV 70 children with no abnormal findings at follow-up).

The average number of symptoms per patient is found, in the mature, to be the highest in Group I (3 6 over 2.1 in Group IV) Moreover there was a clear predominance of specific symptoms in Group I with 92 per cent having one or more such features over about 40 per cent of the mature children in the remaining groups and about 25 per cent among the pre mature in all groups.

An evaluation of the prognostic significance of each symptom and combination of symptoms in the full-term infants gave the following results. In the presence of a single symptom—whether specific or non-specific—the prognosis was relatively good, with a less than 10 per cent risk of severe cerebral sequelae and a 50 per cent chance of a perfectly normal development (75 per cent, if including Group III with dubious sequelae) The rates were essentially similar in the presence of two neonatal symptoms, even including one specific, and in the presence of three non-specific symptoms. When two specific symptoms were combined, the outlook appeared to be worse, with about a 30 per cent risk of severe cerebral sequelae. With an increasing number of symptoms, especially specific symptoms, the prognosis worsened. With a combination of not less than three symptoms, at least one being specific, there was a 40–60 per cent risk of severe sequelae and as high as 60–80 per cent, if no less than two of the symptoms were specific.

Cyanotic attacks—in association with other symptoms—when beginning during the first day of life and persisting beyond the fourth day were a grave prognostic sign. Delayed cyanotic attacks were prognostically unfavourable if persisting for more than 2 days, while attacks limited to one day had no serious implications.

Convulsions appeared to imply a fairly grave outlook, even when limited to one or two days more so when persisting for more than three days.

In the premature the evaluation was somewhat difficult because so few patients survived the neonatal period, and partly because the premature mostly exhibited very few symptoms, in particular very few specific symptoms. It was found, however that as many as three symptoms, even when one or two were specific, did not always imply a grave prognosis.

The role of aetiological factors as related to the diagnostic and prognostic

value of the neonatal symptoms is the main subject of *Chapter VI* which deals with conditions during pregnancy and delivery as well as with the occurrence of asphyxia. Asphyxia here is defined as delayed initiation of spontaneous breathing following birth.

Complications of pregnancy were reported in 12 per cent of the mothers and was thus too rare to allow conclusions as to their significance. It was, however evident that complications of pregnancy had no decisive influence on the frequency of complications of delivery nor of asphyxia.

Complications of delivery occurred in 44 per cent of the cases, or twice as often as in a normal population.

35 per cent of the children had been asphyxiated. (The incidence of asphyxia in unselected obstetric series is found to be 2–6 per cent) In the present material asphyxia occurred twice as often following a complicated delivery as following a normal delivery

In 50 per cent of the cases pregnancy and delivery were normal, and in two-thirds of these the infants did not exhibit asphyxia. The neonatal symptomatology of this group did not differ from that of the group of non-asphyxiated infants whose birth was complicated, nor did their prognosis differ with any certainty

In the presence of asphyxia, following normal as well as complicated deliveries, there was a slight increase in the number of neonatal symptoms, mainly of those specifically cerebral in origin. This was paralleled by a graver prognosis following asphyxia of short duration. Asphyxia, when persisting for more than five minutes, was associated with a high neonatal mortality rate.

The course of the delivery apparently had some bearing on the prognostic value of the neonatal symptoms in so far as a child whose birth was normal, who exhibited two or three neonatal symptoms including one or two specific symptoms, more often would have an unfavourable prognosis than a patient with the same combination of symptoms following a complicated delivery This was true regardless of the course of pregnancy or of the occurrence of asphyxia.

In 72 of the 122 fatal cases both pregnancy and delivery had been uncomplicated. In 55 per cent autopsy disclosed intracranial haemorrhage. In 41 fatal cases the delivery had been complicated 85 per cent of these had intracranial haemorrhage. No symptomatological differences were demonstrable.

Firstborn infants were found on average to have slightly more specific symptoms than children of multiparas, and this was paralleled by a higher incidence of sequelae. Children of elderly primiparas did not differ symptomatologically from children of younger primiparas however they had a less favourable long-term prognosis.

The available data on the administration of labour stimulating drugs was scanty and has been only briefly mentioned. It was noted that children born by induced or stimulated deliveries, the course of pregnancy and delivery being otherwise normal, seemed to do less well than children born by non-stimulated normal deliveries.

Previous studies on the prognostic significance of the perinatal condition are reviewed. Opinions have varied considerably as to the influence of birth injury and of asphyxia. However, these divergencies may be explained to a large extent by differences in the selection of materials. The course of delivery though not all-important, seems in certain cases to be of primary importance for the development of later cerebral defects. Asphyxia is commoner following complicated deliveries than following normal deliveries. In severe cases it is often associated with neonatal death in milder cases cerebral sequelae are quite frequent. However the neonatal symptoms seem to give more reliable indications for the prognosis than the course of delivery and asphyxia.

Chapter VII deals with aspects of prematurity The rate of prematurity was very high (35 per cent over about 7 per cent in a normal population) and the neonatal mortality rate was considerably higher (70 per cent) than among the mature patients (31 per cent) the lower the birth weight, the higher the mortality

On the other hand no late-prognostic differences were demonstrated between premature and mature children. (31 per cent of the former and 35 of the latter had severe or minor cerebral sequelae)

Symptomatologically the premature differed from the mature in exhibiting fewer neonatal symptoms. This was more pronounced the lower the birth weight.

A review is given of previous studies on the prognosis of premature children. The materials, however are not directly comparable owing to varying criteria of selection and varying follow-up rates. It is evident, though, that among premature children with very low birth weights, or presenting neonatal cerebral symptoms, there was a higher percentage of cerebral sequelae than among premature children with higher birth weights or presenting no evidence of cerebral injury Hence it is concluded that the sequelae observed in the present series are due to neonatal cerebral influences rather than to prematurity itself

Chapter VIII Sex differences are mentioned briefly There was a majority of boys (63 per cent) but no differences were found in neonatal mortality or long-term prognosis of boys and girls. Among the neonatal fatalities there was a significantly higher incidence of cerebral oedema in the boys. No explanation can be offered for this finding.

Resumé

Formålet med arbejdet har været at vurdere neonatale, formodet cerebrale symptomers specificitet og prognostiske værdi.

I *kapitel I* gennemgås den tidligere litteratur angående cerebrale symptomer hos nyfødte med hensyn til de arbejder hvor klinik og pathologi er sammenholdt. Det fremhæves, at den kliniske diagnosticering af hjerneskader hos nyfødte er vanskelig, fordi de frembudte symptomer ofte er uspecifikke og fordi mange patienter kun frembyder meget få symptomer De oftest registrerede symptomer er cyanose, respirationsuregelmæssigheder bevidstheds- og tonusændringer krampe og manglende drikkeevne. Ingen af disse er dog fundet 100 % specifikt cerebrale.

Desuden omtales tidligere arbejder om prognosen ved intracranielle, neonatale lidelser Materialerne er vanskeligt sammenlignelige, primært p. gr. a. forskelle i udvælgelseskriterier men også p gr a. stor variation i efterundersøgelsesprocent og i børnenes alder ved efterundersøgelsen. Trods dette varierede frekvensen af fundne, svære cerebrale følgetilstande kun mellem ca. 10 og 30 % Derimod viste der sig stor uenighed om, hvilke kliniske symptomer der kunne tillægges størst prognostisk betydning og nogen entydig konklusion kunne ikke uddrages

Man omtaler derefter flere nyere undersøgelsesprincipper hvor der lægges stor vægt på den neurologiske undersøgelse neonatalt. Den prognostiske betydning af disse undersøgelser vil først kunne endeligt vurderes, når langtidsefterundersøgelser har fundet sted

I *kapitel II* beskrives eget materiale Det består af 291 børn indlagt i neonatalperioden på børneafdelingen, Københavns Amts Sygehus i Gentofte. Udgangspunktet for undersøgelsen er journalmateriale udvalgt efter diagnoser der 1) enten sandsynliggjorde cerebral beskadigelse, hæmorrhagia intracranialis, partus difficilis seq fractura cranii eller asphyxia neonatorum eller 2) med hvilke patienterne kunne forventes at frembyde en del af de samme symptomer som første gruppe. Disse diagnoser var atelectasis pulmonum aspiratio ad pulmonum eller debilitas congenita. Andre patienter som kunne have haft samme symptomer men hvor anden, sikker diagnose

var givet f. eks. verificeret mb. cordis eller hiatus hernie er ikke medtaget. Det samme gælder patienter med sværere neonatal icterus. Foruden de neonatale symptomer og det kliniske forløb under indlæggelsen, blev graviditets- og fødselsforløb registreret så udførligt som oplysningerne tillod.

Det hyppigst forekommende neonatale symptom var cyanose, som fandtes hos 3/4 af patienterne. Respirationsforstyrrelser og slaphed forekom hos godt 1/2, krampe hos knapt 1/4 og sitren, irritabilitet og rigiditet hos knapt 1/5 af patienterne. Symptomerne optrådte i talrige kombinationer. Gennemsnitligt havde hver patient 2,5 symptom. De præmature patienter som udgjorde 35 % af materialet, havde lidt lavere symptomfrekvens (2,3 symptom/patient) end de mature (2,7 symptom/patient). De præmature havde relativt sjældnere end de mature symptomerne krampe, sitren, irritabilitet og rigiditet.

Patienterne var indlagt i årene 1946–1955. Efterundersøgelsen fandt sted i 1958–59. Seksten børn er udgået af undersøgelsen p. gr. a. manglende oplysninger om deres senere udvikling. Tolv var døde efter udskrivelsen, men indgår i undersøgelsen, da man havde tilstrækkelige oplysninger om deres udvikling og for en dels vedkommende fyldige sektionsbeskrivelser. Om 6 børn foreligger kun skriftlige oplysninger fra forældre og/eller behandlende læge om den senere tilstand. De øvrige er undersøgt af forf. Efterundersøgelsesprocenten er således 95.

Ved efterundersøgelsen foretoges en almen klinisk og en neurologisk undersøgelse, samt en psykisk vurdering. Der blev optaget en grundig anamnese med speciel vægt lagt på psykisk, motorisk og somatisk udvikling. Desuden indhentedes oplysninger om specielle undersøgelser foretaget før efterundersøgelsen (psykologisk testning, øjenundersøgelse, otologisk undersøgelse, talemæssig vurdering og eeg.). I enkelte tilfælde, hvor det skønnedes indiceret og var praktisk gennemførligt, blev ligneende undersøgelser foranlediget gjort.

I beskrivelsen af *efterundersøgelsens resultater* er patienterne inddelt i neonatalt døde og 4 grupper overlevende.

122 = 44 % af patienterne døde neonatalt. Makroskopiske sektionsbeskrivelser foreligger for alle 122 patienter og der gøres rede for de påviste dødsårsager og andre abnorme fund. Hos 84 % fandtes hæmorrhagia intracranialis, ødema cerebri eller en kombination heraf som primær dødsårsag. Seksten procent var døde af atelectasis pulm. og havde ingen abnorme hjernefund.

29 = 11 % (= 19 % af de patienter der overlevede neonatalperioden) havde svære cerebrale følgetilstande: 18 patienter var oligofrene og havde svære neurologiske symptomer, 7 var oligofrene og motorisk retarderede i varierende grad og 4 var normalt begavede, men havde neurologiske symptomer. Tolv af de oligofrene patienter var døde, de fleste i alderen 2–3 år. Kramper forekom hos 16 patienter, talemæssig retardering hos 21, hørened-

sættelse hos i hvert fald 5 og strabismus hos 15 patienter Der gøres rede for electroencephalografiske fund (hos 21 patienter) luftencephalografi (hos 13 patienter) og fund ved hjernesektion (hos 7 patienter) samt cranieomfangsmål (hos 20 patienter) Der blev fundet tegn på cerebral atrofi hos 21 af disse 29 patienter

24 = 9 % (= 16 % af de patienter der overlevede neonatalperioden) havde lettere cerebrale følgetilstande i form af lettere psykisk retardering, forbigående retarderet motorisk udvikling eller trivsel gentagne krampeanfald – afebrile eller febrile – høredefekter afasi eller talemæssig retardering, forbigående hyperaktivitet i de første 1–2 leveår adfærdsvanskeligheder strabismus og enuresis Alle havde mere end eet af disse symptomer og symptomkombinationerne var varierende. Ingen havde blivende motoriske handicaps.

30 = 11 % (= 19 % af de patienter der overlevede neonatalperioden) havde lette, formentlig cerebrale afvigelser af samme karakter som i ovennævnte gruppe, men mindre udtalte, og de fleste af patienterne frembød kun et enkelt symptom. I denne gruppe var desuden 5 tilfælde af dyslexi, men ingen tilfælde af intelligensdefekt, afebrile kramper eller hørenedsættelse.

70 = 25 % (= 46 % af de patienter der overlevede neonatalperioden) frembød ingen abnorme fund.

Berettigelsen af at sætte de ved efterundersøgelsen fundne abnormiteter i relation til den neonatale tilstand diskuteres med henvisning til litteraturen. Man mener at kunne finde fuld støtte for de senere svære cerebrale symptomers vedkommende og tilstrækkelig for de lettere symptomers vedkommende til med nogen rimelighed at opretholde antagelsen af en fælles oprindelse.

I *kapitel III* bedømmes de neonatale symptomers diagnostiske værdi ved at sammenligne symptomerne hos følgende patienter døde neonatalt af 1) atelectasis pulm. (normal hjerne) 20 patienter 2) atelectasis pulm. og ødema cerebri, 19 patienter 3) atelectasis pulm. og hæmorrhagia intracranialis ± ødema cerebri, 61 patienter og 4) hæmorrhagia intracranialis ± ødema cerebri (normale lunger) 22 patienter

Symptomerne. krampe, sitren, irritabilitet og rigiditet forekom udeluk kende hos patienter med pathologiske hjernefund. For at sikre værdien af denne iagttagelse er materialet suppleret med yderligere 26 patienter døde neonatalt af atelectasis pulm. Heller ikke disse patienter havde nogen af de ovennævnte symptomer

Selv om disse symptomer i dette materiale således synes specifikt cerebrale, fandtes de på ingen måde nødvendige for at stille diagnosen hæmorrhagia intracranialis eller ødema cerebri. 46 % af de mature patienter og 79 % af de præmature med pathologiske hjernefund frembød kun symptomerne cyanose, respirationsabnormiteter eller slaphed, altså de samme symptomer

som patienter døde af atelectasis pulm. Differentialdiagnosen mellem disse grupper synes meget vanskelig. Permanent cyanose sås noget hyppigere ved de rene atelectaser mens anfaldsvis cyanose var noget hyppigere blandt hjerneskadede; men begge cyanoseformer var så hyppige i begge grupper at forskellen er uden differentialdiagnostisk værdi. Derimod fandtes sene cyanoseanfald (først optrædende i 2.-3 levedøgn) udelukkende i de hjerneskadede grupper.

Det viste sig ikke muligt klinisk at skelne patienter med hjerneødem fra patienter med hjerneblødning. Alle symptomer optrådte med samme hyppighed i de 2 grupper. Der fandtes ingen forskel i optræden af permanent eller anfaldsvis cyanose eller i tidspunktet for cyanosens start. Det samme gjaldt for tidspunktet for optræden og for varighed af krampeanfald. Materialet er suppleret med 41 patienter døde neonatalt af hjerneødem uden at resultatet ændrede sig.

De neonatale symptomers betydning for den umiddelbare prognose quo ad vitam behandles i *kapitel IV*. Det vises, at de neonatalt døde patienter gennemsnitligt havde flere symptomer end de overlevende, således at der med øget antal symptomer hos den enkelte patient synes større risiko quo ad vitam. Dette gjaldt for både mature, hvor de neonatalt døde gennemsnitligt havde 3,1 symptom per patient og de overlevende 2,5 og for de præmature, hvor de tilsvarende tal var 2,5 og 1,7 symptom/patient. Dog sås dødsfald både blandt mature og præmature patienter som kun havde haft et enkelt symptom.

Der er foretaget opgørelse over mortaliteten ved hvert enkelt neonatalt symptom, dels hvor det havde optrådt som eneste symptom (hvilket var sjældent) og dels hvor det havde været til stede sammen med andre symptomer. For præmature børn fandtes symptomerne: cyanoseanfald i første døgn, besværet og knirkende respiration, hypotoni og krampe at være alvorlige prognostiske symptomer med en mortalitet på omkring 80 % mens den for mature lå omkring 40 %. For mature børn fandtes cyanoseanfald, der først optrådte efter første døgn at være af alvorligere betydning end cyanoseanfald optrædende fra første døgn. (Mortalitet 56 % mod 27 %).

Den anfaldsvise cyanose var den hyppigste form, den fandtes hos 77 % af alle patienter med cyanose. Den permanente cyanose, der ikke hævedes inden for nogle timer samt udsættende respiration fandtes naturligt nok omtrent ensbetydende med mors neonatalt.

De mere specifikt cerebrale symptomer krampe, sitren, irritabilitet og rigiditet syntes af mindre alvorlig værdi i den umiddelbare prognose for mature (mortalitet 20-30 %) end de mere uspecifikke. For de præmature havde krampe som nævnt en alvorlig prognose. De øvrige 3 specifikke symptomer forekom så sjældent hos de præmature, at deres prognostiske betydning ikke lader sig vurdere.

I *kapitel V* vurderes de neonatale symptomers sen-prognostiske betydning ved sammenligning af disse symptomer hos patienterne i de 4 grupper over levende (I 29 patienter med svære cerebrale følgetilstande, II 24 med let tere cerebrale følgetilstande, III. 30 med lette, formentlig cerebrale afvigelser og IV 70 patienter uden senere abnorme fund)

Det vises, at det gennemsnitlige antal symptomer per patient for de fuldbårne patienter var højst i gruppe I med 3 6 symptom/patient, mens det for patienter i gruppe IV var 2,1 Desuden fandtes en klart hyppigere optræden af de specifike symptomer i gruppe I hvor 92 % havde eet eller flere af disse symptomer mod ca. 40 % af de mature i de øvrige grupper og ca. 25 % af de præmature i samtlige grupper

Der er foretaget opgørelse over de enkelte symptomers og symptomkombinationers betydning hos fuldbårne med følgende resultat: ved tilstedeværelse af et enkelt symptom – specifikt eller uspecifikt – fandtes relativt gode prognostiske muligheder med under 10 % s risiko for svære cerebrale følgetilstande og 50 %'s chance for fuldstændig normal udvikling (75 % hvis gruppe III med de tvivlsomme følgetilstande regnes sammen med de normale) – Praktisk taget identiske værdier fandtes ved tilstedeværelse af 2 neonatale symptomer – også selv om det ene var specifikt – og ved tilstedeværelse af 3 uspecifike symptomer Optrådte 2 specifike symptomer alene syntes prognosen dårligere med ca. 30 % s risiko for svære cerebrale følgetilstande. Med stigende antal symptomer og specielt med stigende antal specifike symptomer fandtes en tiltagende dårlig prognose: ved en kombination af mindst 3 symptomer hvoraf mindst eet var specifikt, fandtes 40–60 % s risiko for alvorlige følgetilstande og op til 60–80 % hvis mindst 2 af symptomerne var specifike.

Cyanoseanfald – i forbindelse med andre symptomer – optrædende fra første levedøgn, er fundet at have dårlig prognostisk betydning, hvis anfaldene strækker sig ud over 4 døgn Sent optrædende cyanoseanfald syntes allerede at være af dårlig prognostisk betydning, hvis de strækker sig ud over 2 døgn mens cyanoseanfald inden for et enkelt døgn ikke syntes af alvorlig betydning.

Krampeanfald syntes forbundet med ret stor risiko for dårlig prognose, også selv om de kun optræder inden for 1–2 døgn, men oftere hvis de strækker sig ud over 3 døgn.

For præmature patienter har forholdene været meget vanskelige at vurdere, dels p. gr a. det beskedne antal patienter der overlevede neonatalperioden, dels fordi de præmature oftest havde meget få og specielt meget få specifike symptomer Dog fandtes det, at helt op til 3 symptomer selv når 1 eller 2 var specifike, ikke var ensbetydende med en dårlig prognose.

Primært for at se om etiologiske forskelle skulle ændre de neonatale symptomers diagnostiske og prognostiske værdi gøres i *kapitel VI* rede for for

hold under graviditet og fødsel samt for tilstedeværelse af asphyxi. Ved asphyxi er forstået forsinket igangsættelse af den spontane respiration efter fødslen.

Graviditetskomplikationer forekom hos 12 % af mødrene, altså så sjeldent at man ikke kunne vurdere deres betydning i denne henseende. Dog fremgik det, at graviditetskomplikationer ikke på afgørende måde ændrede frekvensen af fødselskomplikationer eller af asphyxi.

Komplikationer under fødslen forekom hos 44 % d. v. s. dobbelt så hyppigt som i en normalpopulation.

35 % af børnene havde været asphyktiske. Frekvensen af asphyxi er i litteraturen i undvalgte obstetriske materialer *fundet til 2–6 %*. Asphyxi forekom i dette materiale dobbelt så hyppigt efter kompliceret som efter normal fødsel.

50 % af patienterne havde helt blanke graviditets- og fødselsanamneser og 2/3 af disse havde heller ikke været asphyktiske. Det fandtes, at denne gruppe patienter ikke adskilte sig i sin neonatale symptomatologi, ej heller sikkert prognostisk fra den gruppe ikke-asphyktiske patienter som havde haft komplikationer under fødslen.

Både efter normal og efter kompliceret fødsel fandtes tilstedeværelse af asphyxi at give gennemsnitligt lidt flere neonatale symptomer en tilvækst, der stort set faldt på de specifikt cerebrale symptomer. Parallelt hermed fandtes dårligere senprognose efter kortvarig asphyxi. Efter asphyxi af over 5 min. s varighed fandtes høj neonatal mortalitet.

Fødselsforløbet syntes til en vis grad at ændre de neonatale symptomers prognostiske værdi, således at en patient, som efter en normal fødsel havde haft 2–3 neonatale symptomer hvoraf 1–2 var specifikt cerebralt, oftere ville have en dårlig prognose end en patient med samme symptomkonstellation efter en kompliceret fødsel. Dette fandtes uafhængigt af graviditetsforløb eller tilstedeværelse af asphyxi.

72 af de 122 neonatalt døde børn var født på normal vis og efter ukompliceret graviditet; hos 55 % af disse fandtes intracraniel hæmorrhagi ved sektion. 41 neonatalt døde patienter havde haft komplicerede fødsler 85 % af disse havde intracranielle blødninger Der påvistes ingen sikre symptomatologiske forskelle.

Førstefødte børn fandtes at have gennemsnitligt lidt flere specifike symptomer end børn af flergangsfødende mødre og parallelt hermed en dårligere senprognose. Børn af ældre førstegangsfødende mødre adskilte sig ikke symptomatologisk fra børn af yngre førstegangsfødende, men havde en dårligere senprognose.

Brugen af vestimulerende midler var meget dårligt belyst og omtales der for kun kort. Det bemærkes, at børn født efter igangsat eller stimuleret fødsel, hvor forhold under graviditet og fødsel iøvrigt var angivet normale, syn-

tes at klare sig dårligere end børn født efter ikke stimuleret, normal fødsel.

Tidligere arbejder om perinatale forholds prognostiske betydning omtales. Der fremdrages stærkt divergerende opfattelser både af fødselstraumers og asphyxis betydning, forskelle som dog nok i væsentlig grad skyldes forskelle i materialeudvælgelse. Fødselsforløbet synes ikke altafgørende men dog i visse tilfælde af primær betydning for senere cerebrale defekter. Asphyxi findes hyppigere efter komplicerede end efter normale fødsler og fører i sine svære grader ofte til mors neonatalt og giver i sine lettere grader ret ofte cerebrale følgetilstande. Dog synes neonatale cerebrale symptomer at give sikrere prognostiske holdepunkter end fødselsforløb og asphyxi.

I *kapitel VII* omtales præmaturitetsproblemet. Præmaturitets-frekvensen var meget høj (35 % mod ca. 7 % i normalbefolkningen) og de præmatures neonatale mortalitet betydeligt højere (70 %) end de matures (31 %) højere jo lavere FV.

Derimod påvistes ingen sen prognostiske forskelle mellem præmature og mature (31 % af de præmature og 35 % af de mature havde svære eller lettere cerebrale følgetilstande).

Symptomatologisk adskilte de præmature sig fra de mature ved at frembyde færre neonatale symptomer: dette vises at blive mere udtalt jo lavere FV.

Der gives en oversigt over tidligere arbejder om præmatures prognose. Også disse arbejder er vanskeligt sammenlignelige primært p. gr. a. forskelle i materialeudvælgelseskriterier og efterundersøgelsesprocent. Dog fremgik det, at der blandt præmature, som neonatalt havde haft cerebrale symptomer eller som havde haft meget lav FV, fandtes højere procent af patienter med cerebrale følgetilstande end blandt præmature med højere FV eller uden neonatale tegn på cerebral skade. Man konkluderer derfor at de påviste følgetilstande i dette materiale skyldes de neonatale, cerebrale påvirkninger snarere end præmaturiteten som sådan.

Kapitel VIII Forholdet mellem drenge og piger omtales desuden kort. Der var i materialet en overvægt af drenge, men der påvistes ingen forskel i neonatal mortalitet eller i sen-prognose. Blandt de neonatalt døde fandtes en signifikant større frekvens af hjerneødem hos drenge end hos piger. Det fandtes ikke muligt at give nogen forklaring herpå.

Case Reports

No. 1 (record 258/3/1947)

A boy born at term in private clinic, on June 25, 1947 to 39 year old multipara following an uncomplicated pregnancy. The delivery was induced by quinine and injections; the course was uncomplicated. The infant was not asphyxiated, but was admitted to the Department of Paediatrics (DPGe) The Copenhagen County Hospital at Gentofte (KASGe) on the second day because of poor sucking. During the third day of life he suffered several convulsions associated with short spell of fever. No other abnormalities were noted except poor growth for about two weeks. He was discharged when 16 days old apparently in good condition.

Diagnoses: eclampsia, intracranial haemorrhage.

At the age of about one year he was referred to the Out Patient Department of the University Clinic of Paediatrics at Rigshospitalet (RH) because of retarded development.

Examination at this time showed him to be severely retarded. He was unable to sit up or to hold his head. H had bilateral tightness of the heel cord. His muscle tone could not be assessed. There was pronounced squint. Prior to admission he had shown occasional "twitchings". Placement under the National Service for the Mentally Retarded (Statens Andssvageforsorg = SA) was recommended, the diagnoses being mental deficiency sequelae of intracranial haemorrhage. Additional diagnoses were: symptomatic epilepsy spastic quadriplegia.

There was no family history of cerebral disease.

It is not known whether the recommendation was followed or not.

The patient died in 1949 when about 2 years old. Post mortem was not performed.

No. 2 (1193/3/1950)

A girl, born at term in a private clinic, on March 12, 1949 to a 37-year old primipara, following normal pregnancy. The delivery lasted for more than two days, and forceps were used because of feeble labour. Labour-inducing drugs had apparently not been given. No information is available on the use of morphia. The cord was wound around the child's neck five times; she did not breathe for seven minutes, was given 0.3 ml lobeline and immediately transferred to the DPGe, where she remained for 33 days. On the first day of life she was given nikethamide and lobeline. During the first week she had repeated convulsions, was rigid and sucked poorly. Her general condition was poor during the first month, then improved, and on discharge it was described as good.

Diagnosis: intracranial haemorrhage.

The parents suspected that something was wrong when the child was unable to focus or sit up at the age of 7–8 months. When she was one year old, they consulted the Neuropaediatric Out Patient Clinic (NPO) of the RH, where she was subsequently treated.

She sat at 14 months, stood with support at two years, walked with support at

5¹/ years and took a few steps unaided at 6 /₂. Her motor pattern was characterized by pronounced imbalance as well as poor coordination of all extremities.

Mental development was severely retarded she had a violent temper and was hard to keep occupied. At the age of 8 years she was placed under the SA. She attended a daily kindergarten for retarded children

During her second year of life she had several convulsions in association with fever At the age of seven years she again had repeated generalized clonic convulsions unprecipitated by fever Anti-convulsant therapy was initiated at this time. On the last examination at the RH at the age of 8 years she had been seizure-free for about 6 months. EEG first performed at 4 years of age, was severely abnormal, with spikes and spike-waves, especially in the right parietal tracing. The last EEG, at 8 years, was still severely abnormal.

Speech development had been relatively good. She began to form sentences at the age of 2 years and talked quite intelligibly by the time she was seven. Her hearing was felt to be normal. She had a squint and nystagmoid eye movements, and her vision was apparently diminished.

There was no family history of cerebral disease.

At follow-up, when she was about 10 years old her general condition was good. Her height was 5 cm above average however her weight was 6 kg below normal. Mental development appeared severely retarded However her speech was essentially normal apart from a stutter and a somewhat limited vocabulary The squint and nystagmoid eye movements persisted. Her head was small, with a circumference of 47.5 cm. Her motor pattern was rather ataxic and neurological examination revealed additional slight spasticity There were no contractures of the limbs.

Diagnoses: spastic quadriplegia, ataxia, mental deficiency microcephaly symptomatic epilepsy strabismus.

No 3 (582/3/1950)

A boy born on Sept. 22, 1950, to a primipara. The pregnancy had been uncomplicated. The delivery took place at home at term and was normal. No record of labour inducing methods or morphia. The patient was asphyxiated for "a few minutes he was treated with contrast baths and injections of unknown type and immediately admitted to the DPGe, where he remained for 24 days. He was very flaccid on admission, but soon developed rigidity and hyperirritability During the first 6 days several convulsions occurred A lumbar puncture was performed the spinal fluid was straw-coloured. The rigidity eventually diminished his general condition improved and he started to gain weight.

Diagnosis: intracranial haemorrhage.

At 6 weeks of age the convulsions recurred and he was readmitted to the DPGe. On admission his general condition was poor and there was pronounced rigidity Lumbar puncture again was performed. The spinal fluid was yellow Two days later he was transferred to the neurosurgical department of the RH. However before further investigation could be carried out, his condition deteriorated and because of severe signs of ileus he was transferred to the Dept. of Paediatrics at the RH where he died the following day Age at death was two months.

There was no history of cerebral disease in the family

Post mortem revealed volvulus colon sigmoidei and perforation of the rectum. Brain section showed multiple cysts of varying age, some quite recent. In some areas of the cortex there was total destruction of ganglion cells with proliferation of glial tissue, but no inflammatory processes.

Diagnoses: spastic quadriplegia and symptomatic epilepsi.

No 4 (1403/3/1951)

A girl, a first child, born on April 20, 1951 The pregnancy had been normal until 3 weeks before delivery when the mother sustained an abdominal injury followed by

vomiting, but no further complaints. The delivery took place at home and was induced by injections. It was reported to have been prolonged, and the heart sound had been affected towards the end. The patient exhibited prolonged asphyxia and did not cry until an hour after birth. She was treated with contrast baths and stimulant injections. On the second day she was admitted to DPGe because of flaccidity: she also had grunting respiration and was given oxygen for several hours. Over the next few days the flaccidity was succeeded by hypertonicity which, however, had disappeared when she was discharged in apparently good condition after 16 days.

Diagnosis: intracranial haemorrhage.

Delayed development was suspected by the parent when she was unable to sit up at the age of twelve months and also had clumsy hand movements. Her growth was good despite difficulty in swallowing and later also in chewing.

She could sit alone when 18 months old, walked with support at three years and alone when about 4 years. Her gait was unsteady broad-based and with high knee-raisings. Her hand movements were also unsteady

When nearly 3 years old she was examined at the NPO of the RH, where her condition was diagnosed as quadriplegia with mild ataxia. On re-examination at the age of 4 the former diagnosis was abandoned, the latter maintained.

Her mental development, as judged by her ability to comprehend situations, was essentially normal at the age of 5 and at the last examination, at the age of 7 her condition had further improved, mentally as well as somatically. She had not, however attained the development appropriate to her age. Her speech was obviously retarded, she had prattled by 6 months, said few words at 3 years, but at the age of 7 was still unable to form sentences. Speech comprehension was correspondingly poor. She had repeatedly been examined by a speech therapist from the State Institute for Speech Disorders, who diagnosed receptive and expressive aphasia. An otologist found her hearing to be slightly diminished at the age of 7 years.

An evaluation of her mental condition had been difficult owing to multiple handicaps. Proper testing was not performed. At 10 years an application submitted for education at a State School for the mentally retarded was rejected, as the child was considered too bright. At the age of 13 she was rejected at school for the handicapped due to feeblemindedness. In the same year she was accepted for a trial period as a pupil at the State Institute for Speech Disorders.

Diagnosis: mental deficiency (?), ataxia, receptive and expressive aphasia, mild hearing loss.

There was no history of cerebral disease in the family

EEG: 1) at 3 years: severely abnormal with generalized spikes, yet predominantly posteriorly over the left occipital region. 2) at 6 years: severely abnormal, very irregular tracing with change in frequency. Considerable spike activity mainly in the form of single spikes of high amplitude, often universally synchronous, but with a clear predominance over the right parieto-occipital region. No accentuation of the changes was seen during photic stimulation. During sleep the focal character was somewhat less pronounced and the abnormal pattern consisted of spike-waves of 2-3 per sec. of very high amplitude.

N 5 (2009? 3.1952)

A boy born on Febr. 26, 1952 to a 32 year old primipara following normal pregnancy. The delivery took place in private clinic. It was induced, presumably on the suspicion of rachitic pelvis; it was prolonged, but otherwise uncomplicated. The BW was 3400 g. There was asphyxia for a few minutes, during which lobeline, mg) was given. On the second day the infant was transferred to DPGe suspected of intracranial injury because of poor sucking and tremor. During the first few days he was found to be rigid; however, the tone subsequently became normal. The neonatal period was complicated by pyloric stenosis, for which surgery was successfully performed. He was discharged after 36 days, apparently in good condition, though nystagmus was noted.

Diagnosis. intracranial haemorrhage.

During the first 10 months of life there was practically no motor or mental progress, however his growth was satisfactory The nystagmus persisted and a squint was also noticed

At ten months he was readmitted to the DPGe with severe meningitis and a history of convulsions for one week. During the acute illness he developed severe spasticity of all four limbs as well as a pronounced hydrocephalus. He remained an in-patient for one year during which time his progress was unsatisfactory There was no motor development and he was unresponsive. He was treated with phenobarbitone for acute restlessness. When about two years old he was placed in an institution for mentally defectives (Andersvænge). During the next six months there were four generalized seizures and numerous episodes of withdrawal or loss of consciousness lasting as long as 24 hours. After going downhill he died aged 2⁹/₁₂ years from bacillary dysentery

Post mortem was not performed owing to the refusal of the parents.

Diagnoses. idiocy acquired hydrocephalus, acquired quadriplegia, symptomatic epilepsy strabismus.

There was no family history of cerebral disease.

No 6 (2801/3/1952)

A boy born as second twin on May 4, 1952, to a multipara following an uncomplicated pregnancy The delivery took place at home and apparently was normal. The twins were monozygotic; the brother was well. The patient was admitted to the DPGe at 11 days because of poor growth which persisted for two weeks. Subsequently his growth was satisfactory and the infant was otherwise normal He was discharged after 25 days in apparently good condition.

Diagnosis. congenital debility

The patient's development was evidently slower than that of the twin brother At six months he experienced a convulsion associated with fever and six months later another convulsion, this time unassociated with fever At 18 months he was readmitted following a third, afebrile, seizure. He was found to be physically and mentally retarded and was thought to have a mild quadriplegia.

EEG at 18 months showed multiple focal abnormalities suggesting generalized organic brain damage.

He walked at about 2¹/₄ years and said single words at about two years. At about three years he experienced a severe convulsion following premedication prior to surgery for hydrocele. Hereafter there was pronounced leftsided hemiparesis and aphasia. At about the age of four he was admitted to a neurosurgical department, Bispebjerg Hospital. A ventriculography was performed, revealing enlargement of the entire ventricular system, more so on the right side. There was copious air over the convexity on the left side, none over the right. Radiological diagnosis was cerebral atrophy Arteriography on the right side showed shift to the right of the anterior cerebral artery no malformation the blood flow was slower than normal (no explanation).

In spite of anti-convulsant drugs the child had seizures approximately twice a year

The parents did not wish to attend the follow-up examination.

There was no familial history of cerebral disease.

Diagnoses: Mental deficiency acquired aphasia, congenital mild spastic quadriplegia, acquired left sided spastic hemiplegia, symptomatic epilepsy

No 7 (2735/3/1952)

A boy born to a primipara on May 13 1952, following an uncomplicated pregnancy The delivery took place in a private clinic, was induced at term and energetically stimulated. Moreover pethidine was given on two occasions. The course was otherwise uncomplicated and not prolonged. The child was asphyxiated for 5 minutes and was brought to the DPGe approximately one day old because of persisting cyanosis.

On admission he was also flaccid. The cyanosis subsided following oxygen therapy and he was discharged three days later in apparently good condition.

Diagnosis: asphyxia neonatorum.

The parents suspected retarded development when the child was unable to sit up at the age of one year. They also found him mentally retarded. He was brought to the NPO of the RH, where he was followed-up at intervals. On the last occasion, at the age of 6½ years, he showed moderate spasticity most pronounced in the legs.

He was able to sit alone at 15 months, began to walk alone at 29 months and eventually walked fairly well. Mental development was also retarded. Psychological testing had been attempted repeatedly but was difficult. When last tested, at the age of 6½, the child's intelligence was found to equal that of a 4–5 year old. He also had speech disorder. On the last examination his vocabulary was very limited and the formation of sentences was poor. His hearing was considered to be normal, his vision was good, but he had a squint. Head circumference on all examinations had been below the limit of normal; the shape of his head was otherwise normal.

No family history of cerebral disease was elicited.

Diagnoses: mental deficiency, spastic diplegia, speech retardation, microcephaly, convergent strabismus.

No. 8 (3691/3/1952)

A boy, first child, born at term in a private clinic on May 19, 1952, following an uncomplicated pregnancy. The delivery was induced and took a normal course, however manual expulsion was performed. There was asphyxia for a few minutes, during which lobeline was given. He was immediately referred to the DPGe suspected of tentorial rupture. On admission he was restless, trembling and rigid. From the second to the fourth day repeated attacks of cyanosis and convulsion occurred. His growth was poor during the first two weeks, but eventually improved. When discharged after 3 weeks there was still moderate rigidity.

Diagnosis: intracranial haemorrhage.

At home he was restless and therefore referred to the OP of the DPGe 3 months old. He exhibited spasticity in all four limbs.

His motor development was very unsatisfactory. He was never able to sit up or stand and control of headmovements was poor. His growth was slow and he was difficult to feed. He exhibited a squint. He was also mentally retarded, though he did appear to have some contact with his surroundings. He could smile, and at 18 months was able to say a few words. At this time he came under the care of SA and was placed in an institution (Andersvænge), where he died one year later.

There was no family history of cerebral disease.

Brain section (by Dr. Erna Christensen): Weight of the fixed brain 1050 grams. Moderate dilatation of the ventricles, no necrotic processes, but some atrophy of the basal ganglia. Sclerosing pyknotic ganglion cells, particularly in the putamen and the adjacent thalamus, with occasional intracellular calcification. Degeneration of myelin sheaths in the same area. Normal ganglia in the hypothalamus. Normal cortex, medulla oblongata and cervical medulla. Diagnoses: congenital dysplasia of the cerebrum, chronic degeneration of the basal ganglia. Possible anoxic aetiology.

No. 9 (1470/3/1952)

A boy born in hospital on Dec. 6, 1952, to a 16 year old unmarried primipara. During the delivery, which was uncomplicated, quinine and pituitrin was administered. The BW was 1500 g. There was no *asphyxia*. *Immediate* referral to the *DPGe because* of low BW. On admission the child's respiration was grunting, and during the next 25 days there were numerous severe cyanotic attacks of diminishing frequency during which he was considered moribund several times. In such cases lobeline was given. He received oxygen *for four* weeks, after which it was withdrawn over three weeks under regular eye observation. Four days before oxygen was discontinued,

Diagnosis: intracranial haemorrhage.

During the first 10 months of life there was practically no motor or mental progress, however his growth was satisfactory The nystagmus persisted and a squint was also noticed.

At ten months he was readmitted to the DPGe with severe meningitis and a history of convulsions for one week. During the acute illness he developed severe spasticity of all four limbs as well as a pronounced hydrocephalus. He remained an in-patient for one year during which time his progress was unsatisfactory There was no motor development and he was unresponsive. He was treated with phenobarbitone for acute restlessness. When about two years old he was placed in an institution for mentally defectives (Andersvænge). During the next six months there were four generalized seizures and numerous episodes of withdrawal or loss of consciousness lasting as long as 24 hours. After going downhill he died aged 2⁹/₁₂ years from bacillary dysentery

Post mortem was not performed owing to the refusal of the parents.

Diagnoses: idiocy acquired hydrocephalus, acquired quadriplegia, symptomatic epilepsy strabismus.

There was no family history of cerebral disease.

No 6 (2801/3/1952)

A boy born as second twin on May 4 1952, to a multipara following an uncomplicated pregnancy The delivery took place at home and apparently was normal. The twins were monozygotic; the brother was well. The patient was admitted to the DPGe at 11 days because of poor growth which persisted for two weeks. Subsequently his growth was satisfactory and the infant was otherwise normal He was discharged after 25 days in apparently good condition.

Diagnosis: congenital debility

The patient's development was evidently slower than that of the twin brother At six months he experienced a convulsion associated with fever and six months later another convulsion, this time unassociated with fever At 18 months he was readmitted following a third, afebrile, seizure. He was found to be physically and mentally retarded and was thought to have a mild quadriplegia.

EEG at 18 months showed multiple focal abnormalities suggesting generalized organic brain damage.

He walked at about 2¹/₂ years and said single words at about two years. At about three years he experienced a severe convulsion following premedication prior to surgery for hydrocele. Hereafter there was pronounced leftsided hemiparesis and aphasia. At about the age of four he was admitted to a neurosurgical department, Bispebjerg Hospital. A ventriculography was performed, revealing enlargement of the entire ventricular system, more so on the right side. There was copious air over the convexity on the left side, none over the right. Radiological diagnosis was cerebral atrophy Arteriography on the right side showed shift to the right of the anterior cerebral artery no malformation the blood flow was slower than normal (no explanation).

In spite of anti-convulsant drugs the child had seizures approximately twice a year

The parents did not wish to attend the follow-up examination.

There was no familial history of cerebral disease.

Diagnoses: Mental deficiency acquired aphasia, congenital mild spastic quadriplegia, acquired left-sided spastic hemiplegia, symptomatic epilepsy

No 7 (2735/3/1952)

A boy born to a primipara on May 13 1952, following an uncomplicated pregnancy The delivery took place in a private clinic, was induced at term and energetically stimulated. Moreover pethidine was given on two occasions. The course was otherwise uncomplicated and not prolonged. The child was asphyxiated for 5 minutes and was brought to the DPGe approximately one day old because of persisting cyanosis.

On admission he was also flaccid. The cyanosis subsided following oxygen therapy and he as discharged three days later in apparently good condition.

Diagnosis: asphyxia neonatorum.

The parents suspected retarded development when the child was unable to sit up at the age of one year They also found him mentally retarded. *He was brought* to the NPO of the RH, where he was followed-up at intervals. On the last occasion, at the age of 6½ years, he showed *moderate spasticity* most pronounced in the legs.

He was able to sit alone at 15 months, began to walk alone at 29 months and eventually walked fairly well. Mental development was also retarded. Psychological testing had been attempted repeatedly but was difficult. When last tested, at the age of 6½, the child' intelligence was found to equal that of a 4–5 year old. He also had speech disorder On the last examination his vocabulary was very limited and the formation of sentences was poor. His hearing was considered to be normal, his vision as good, but he had squint. Head *circumference* on all examinations had been below the limit of normal, the shape of his head was otherwise normal.

No family history of cerebral disease was elicited.

Diagnosis: mental deficiency spastic diplegia, speech retardation, microcephaly convergent strabismus.

No. 8 (3091/3/1952)

A boy first child, born at term in a private clinic on May 19 1952, following an uncomplicated pregnancy The delivery was induced and took a normal course: *however manual expulsion was performed. There was asphyxia for* few minutes, during which lobeline was given. He was immediately referred to the DPGe suspected of tentorial rupture. On admission he was restless, trembling and rigid. From the second to the fourth day repeated attacks of cyanosis and convulsion occurred. His growth was poor during the first two weeks, but eventually improved. When discharged after 3 weeks there was still moderate rigidity

Diagnosis: intracranial haemorrhage

At home he was restless and therefore referred to the OP of the DPGe 3 months old. He exhibited spasticity in all four limbs.

His motor development was very unsatisfactory He was never able to sit up or stand and control of headmovements was poor His growth was slow and he was difficult to feed He exhibited squint. He was also mentally retarded, though he did appear to have some contact with his surroundings. He could smile, and at 18 months was able to say few words. At this time he came under the care of SA and was placed in an institution (Andersvænge), where he died one year later

There was no family history of cerebral disease.

Brain section (by Dr Erna Christensen): Weight of the fixed brain 1030 grams. Moderate *dilatation* of the ventricles, no necrotic processes, but some atrophy of the basal ganglia. Sclerosing pyknik ganglion cells, particularly in the putamen and the adjacent thalamus, with occasional intracellular calcification. Degeneration *of myelin* sheaths in the same area. Normal ganglia in the hypothalamus. Normal cortex, medulla oblongata and cervical medulla. Diagnosis: congenital dysplasia of the cerebrum, chronic degeneration of the basal ganglia. Possible anoxic aetiology

N 9 (1470/3/1952)

A boy born in hospital on Dec. 6, 1952, to 16 year old unmarried primipara. During the delivery which was *uncomplicated*, quinine and pituitrin was administered. The BW was 1580 g. There was no asphyxia. Immediate referral to the DPGe because of low BW *On* admission the child's respiration was grunting, and *during the next* 25 days there were numerous severe cyanotic attacks of diminishing frequency during
ich he was considered moribund several times. In such cases lobeline was given. He received *oxygen for four* weeks, after which it was withdrawn over three weeks under regular eye observation. Four days before oxygen was discontinued opthalmo-

scopy was normal, but five days after its discontinuation there was marked retrolental fibroplasia. After subsiding to some extent it became stationary. After a while growth became normal, and the infant was discharged after 75 days in apparently good condition, apart from the eye changes. He was placed in a private foster home.

Diagnoses: prematurity, congenital debility, retrolental fibroplasia.

The foster parents consulted the DPGe when the boy was 6 months old because of pronounced strabismus. He was found to be severely retarded, physically as well as mentally. He had a severe spastic quadriplegia, which was attributed to intracranial haemorrhage. There was also a question of possible microcephaly. The retrolental fibroplasia persisted.

At 11 months he was seen at the NPO of the RH. The diagnoses were confirmed except for the eye changes, which had disappeared.

EEG at one year showed a severe focal dysrhytmia with spikes in the left temporal region.

He achieved a developmental quotient of 30 (according to Bühler). One month later he was admitted to hospital (Nørre Hospital) and at the age of 4 years was placed in an institution under SA (Rødbygård). He died at the age of 4 years and 3 months having failed to develop physically in any respect and mentally to only a slight degree. His D.Q. had remained at about 30 on later tests. His growth was poor, he had difficulty in swallowing and was unable to take anything but liquid food. His vision was deficient.

There was no history of cerebral disease in the family.

Post mortem was not performed.

Diagnoses: Idiocy, spastic quadriplegia, microcephaly, strabismus.

No. 10 (1025/3/1953)

A boy born as a first child on Jan. 15, 1953 following a normal pregnancy. Delivery took place at home at term and was prolonged. There is no record of the use of labour inducing drugs or morphia. There was prolonged asphyxia, and the child did not cry until one hour after birth. There is no record of what resuscitation methods were used. He was first admitted to hospital 13 days later because of flaccidity, restlessness and poor growth. On admission he was irritable and flaccid and sucked poorly; from the 14th to the 18th day there was considerable trembling and repeated convulsions. Thereafter the child recovered somewhat and his growth improved. When discharged, after one month's stay, he was still rather apathetic, however, and appeared withdrawn. During admission his head circumference increased by 3 cm (1 cm more than normal rate). Continued follow-up was recommended.

Diagnosis: intracranial haemorrhage.

The child was readmitted at the age of 3 months. His growth meanwhile had been good, but he had been restless and rigid with occasional opisthotonus. He did not recognize his parents and he did not focus. On examination he was found to be rigid and listless. The rigidity was more pronounced on the right side. Head circumference had increased by 10 cm since birth (against a normal increase of 5 cm) and was clearly greater than normal. Ventriculography was performed at 4 months and revealed hydrocephalus with shift to the right of the enlarged ventricular system. On subsequent craniotomy a cyst over the left hemisphere was evacuated. The course was uneventful. Repeat air encephalography at the age of 5 months, again showed dilatation of the ventricular system. The condition did not improve, and the child remained restless and rigid. The temperature fluctuated. Death occurred in hyperpyrexia when the child was 6½ months old. Post mortem was not performed.

There was no family history of cerebral disease.

Diagnoses: internal hydrocephalus, operated, spastic quadriplegia.

No. 11 (1587/3/1953)

A boy born at term at the RH on April 7, 1953 to a multipara, who had suffered from epilepsy since she was 19. The delivery was prolonged, forceps were used. BW

was 4300 grams. The infant was asphyxiated for six minutes and cyanosed for the first few hours. He was trembling and rigid and suffered repeated convulsions during the next few days. The rigidity gradually diminished and had disappeared by the time the infant was transferred to the DPGe at the age of 18 days. He remained in this department only three days and on discharge his condition apparently was good.

Diagnosis: sequelae of difficult birth.

During the following six months he exhibited repeated seizures, until anticonvulsant therapy was instituted.

EEG, at 6 months, showed severe dysrhythmia with numerous spikes and spike-waves.

Both mental and motor development were severely retarded. During the first year of life he was examined at several hospitals, where the diagnoses of mental deficiency and cerebral palsy were made, the type of paresis, however was difficult to determine; spasticity athetosis, ataxia and hypotonia were all considered. At the age of two years he was put under SA and two years later placed in an institution (Ebberødgård), where he still remained at the time of follow-up, when he was 4½ years old. A conclusive neurological diagnosis was difficult even at this point. His muscle tone varied considerably: his motor pattern was that of an infant; and though able to sit up, he could not stand. The picture was somewhat ataxic. There was considerable mental deficiency. He was pleased to have company but recognized none and could not be engaged in any kind of activity. A convergent strabismus was present.

Diagnoses: idiocy, cerebral palsy, ataxia? symptomatic epilepsy, convergent strabismus.

No. 12 (7284/3/1954)

A girl born in a private clinic on March 24, 1954, to a 29 year old primipara. The delivery was induced at term and was normal, pethidine was given, however. The infant was asphyxiated for 20 minutes, in the course of which she was given coramine, lobeline and alternating hot and cold baths. She was immediately transferred to the DPGe suspected of intracranial haemorrhage. She suffered a few cyanotic attacks during the first 24 hours. A cephalhaematoma was found in the right occipital region, but otherwise she was normal and hence was discharged on the third day.

Diagnoses: asphyxia neonatorum, congenital debility.

During the early months of life she exhibited frequent tonic-clonic seizures, sometimes several times daily. Despite intensive antiepileptic therapy the seizures persisted, prompting re-examination at the age of three months. At that time she exhibited pronounced motor hyperactivity and rigidity and at the age of 6 months a diagnosis of spastic quadriplegia was made. She never attained essential motor functions. When she was last seen, at the age of 12 years she could neither sit, nor walk and was completely helpless. She was severely mentally defective, almost unresponsive, had no speech nor comprehension of speech. She was microcephalic, extremely emaciated, but of normal height and pubescence. Though under the care of SA she nevertheless had been looked after at home, until she was institutionalized (at the Children's Hospital in Vangede) at the age of 12 years. Until that time she had been treated at the NPO of the RH.

No family history of cerebral disease was elicited.

Diagnoses: mental deficiency, spastic quadriplegia, symptomatic epilepsy, microcephaly, convergent strabismus.

EEG had been performed as follows: 1) at 9 months: normal, 2) at 20 months: normal, 3) at 26 months: severely abnormal, 4) at 3 years: severely abnormal (1–3 per second focus with bifrontal spikes plus isolated spikes in the left hemisphere. 5) at 5 years: severely abnormal with paroxysmal pattern, 2–6 per second activity of high amplitude, generalized admixture of spikes; slight amplitude predominance on the left side, or depression of activity on the right side.

PEG was performed 1) at 15 months, showing moderate generalized enlargement of the ventricles, 2) at 26 months showing generalized atrophy of predominantly cortical location.

No 13 (781/3/1954)

A girl, born at term at home on April 8, 1954 to a multipara, who had suffered hyperemesis during the first four months of the pregnancy The delivery was stimulated by injections and was very quick The infant was not asphyxiated, but was admitted to the DPGo on her second day of life owing to the occurrence of convulsions. On admission she was found to be restless and rigid, with grunting respiration. Several seizures occurred on the day of admission and the following day but not again. On discharge, at 14 days, she was however still restless, screaming and somewhat rigid

Diagnosis: intracranial haemorrhage.

Following discharge the parents suspected cerebral damage, and due to retarded development the child was brought to the NPO of the RH at the age of 6 months. A diagnosis was made of spastic quadriplegia, presumed mental deficiency and microcephaly Moreover there were nystagmoid eye movements and a squint.

PEG at the age of 14 months revealed severe generalized dilatation of the ventricular system.

Mental development remained severely retarded, though she was not completely unresponsive. Motor development was also severely retarded. At the age of 18 months she was able to sit up supported, but never unsupported. From the age of 12 months she exhibited frequent spells of rapid twitching, often occurring several times daily and provoked by none. She was treated with phenobarbitone.

EEG was characterized by 2–3 per second activity of high amplitude, more so over the right hemisphere and bifrontally There were a number of spikes and spike-waves (single) over the right fronto-temporal region. (The record was unlike hypsarrhythmia).

When 18 months old she was placed under SA and at about 2 years she was institutionalized (Children's Hospital at Nyborg). She died there at the age of 2 /12 years.

There was no history of cerebral disease in the family

Diagnoses. mental deficiency quadriplegia, symptomatic epilepsy microcephaly and strabismus.

Brain section was performed by Dr Erna Christensen. The brain weighed 600 grams following fixation. Its shape was normal, though the cerebrum was considerably smaller than normal. Microgyri were seen all over the convexity though not of uniform distribution. On the lower aspect of the right frontal lobe the gyri were flattened presumably due to enlargement of the anterior horn. The leptomeninges were not thickened. The vessels showed no definite changes. The cerebellum was of normal size and had normal gyri. Frontal section revealed spongy brain tissue with networks of varying size. The degeneration was most pronounced on the convexity and in the anterior two-thirds of the cerebrum there was atrophy of the gyri in the parieto-occipital lobes, but no polyporencephaly was observed. The ventricles were severely enlarged The cystic necrotic processes had invaded the insula and the lateral areas of the corpus striatum in both sides. In the area of the thalamus, at the level of the massa intermedius bilateral atrophy was present in the upper median portions in the form of yellowish necrotic processes. Yellowish discoloration was not observed elsewhere. The remaining areas of the basal ganglia were sclerotic, with blurred outlines. The aqueduct and the fourth ventricle were not enlarged. There was slight granulation in the ependyma on the walls of the lateral ventricles and possibly also in the fourth ventricle. The cerebellum, pons and medulla oblongata were macroscopically normal on the sectioned surfaces.

Pathological diagnosis: pronounced polyporencephaly due to cerebral anoxia.

No. 14 (26001/205/1955)

A girl born in hospital on March 8, 1955, to 30 year old primipara *following* normal pregnancy. The delivery was normal. BW was 3800 g. No asphyxia. Admitted to the DPGs on the second day because of convulsion and suspected intracranial haemorrhage. The convulsion did not recur, but she remained rigid, trembling and with a high-pitched cry until the 10th day. There was a cephalhaematoma in the right side. The eye movements were nystagmoid, and opthalmoscopy showed retinal haemorrhages. On discharge, 14 days later her condition was good, but follow-up was recommended.

Diagnosis: intracranial haemorrhage.

Re-examination at NPO of the RH at 3 months revealed spasticity in all four limbs, restlessness, tremor sensitivity to noise and a squint. Head circumference was normal at this time, but at about 2 years of age it was just below average, and when last seen at well over four years, it was well below the normal limit. At 9 to 10 months she had episodes of jerking in the legs, which did not occur however from her third month she was treated with phenobarbitone and mysoline. Her mental development was slow. At 4 years her speech comprehension was poor and she was able to make only a few sounds. Growth was good during the early months of life, but subsequently poor. Motor function was very defective; when seen last at four years she was unable to sit up alone.—There was no family history of cerebral disease.

Diagnoses: mental deficiency spastic quadriplegia, microcephaly strabismus.

No. 15 (26262/3/1955)

A girl, born at term in a private clinic on March 11 1955 to a primipara, who within the first month of pregnancy had been operated on for corpus luteum cyst. Otherwise the pregnancy was normal. The prolonged delivery was stimulated by 13 or 14 injections because of lack of progress. The heart sound eventually became affected, and the infant was delivered by forceps. She was asphyxiated for an unknown length of time and was admitted to the DPGs during her second day of life because of convulsions and suspected intracranial haemorrhage. On admission she was rigid, restless and screaming, and during the second to fifth day she experienced numerous convulsions. There were also several episodes of harlequin colour change. The rigidity subsided within eight days. However her condition was decribed as unsatisfactory at discharge after 26 days, though no particulars were given. The outlook was considered doubtful.

Diagnoses: intracranial haemorrhage, nystagmus, strabismus.

Her development was severely retarded. At 7 months a diagnosis of spastic quadriplegia was made on O.P. examination at the DPGs. Subsequently she was treated at other hospitals. She achieved no motor function and had hardly any contact with her surroundings. She could smile and focus, however. Her hearing was thought to be impaired and she did not talk. She was very restless. At about 18 months she experienced two episodes of convulsions and from the age of two, or two-and-a-half she exhibited repeated seizures.

EEG at 1 year 7 months showed an atypical pattern with absence of activity in central-parietal and central tracings in *sleep* as well as waking record. Frontal and temporal tracings revealed spikes, more pronounced on the left side.

PEG at the same age disclosed excessive enlargement of the lateral ventricles, the left being larger than the right. No cortical air was seen.

Her growth was poor and she had to be fed by tube most of the time. At about 18 months she was put under SA and at about 2 years she was placed in an institution (Karensminde), where she died of broncopneumonia some seven months later.

There was no family history of cerebral disease.

Diagnoses: mental deficiency spastic quadriplegia, symptomatic epilepsy microcephaly

Brain section was performed by Dr Erna Christensen. The weight of the fixed

PEG was performed 1) at 15 months, showing moderate generalized enlargement of the ventricles; 2) at 26 months showing generalized atrophy of predominantly cortical location.

No 13 (781/3/1954)

A girl, born at term at home on April 8, 1954 to a multipara, who had suffered hyperemesis during the first four months of the pregnancy The delivery was stimulated by injections and was very quick. The infant was not asphyxiated, but was admitted to the DPGe on her second day of life owing to the occurrence of convulsions. On admission she was found to be restless and rigid, with grunting respiration. Several seizures occurred on the day of admission and the following day but not again. On discharge, at 14 days, she was however still restless, screaming and somewhat rigid.

Diagnosis: intracranial haemorrhage.

Following discharge the parents suspected cerebral damage, and due to retarded development the child was brought to the NPO of the RH at the age of 6 months. A diagnosis was made of spastic quadriplegia, presumed mental deficiency and microcephaly Moreover there were nystagmoid eye movements and a squint.

PEG at the age of 14 months revealed severe generalized dilatation of the ventricular system.

Mental development remained severely retarded, though she was not completely unresponsive. Motor development was also severely retarded. At the age of 18 months she was able to sit up supported, but never unsupported. From the age of 12 months she exhibited frequent spells of rapid twitching, often occurring several times daily and provoked by noise. She was treated with phenobarbitone.

EEG was characterized by 2–3 per second activity of high amplitude, more so over the right hemisphere, and bifrontally There were a number of spikes and spike-waves (single) over the right fronto-temporal region. (The record was unlike hypsarrhythmia).

When 18 months old she was placed under SA and at about 2 years she was institutionalized (Children s Hospital at Nyborg). She died there at the age of 2³/₁₂ years.

There was no history of cerebral disease in the family

Diagnoses: mental deficiency quadriplegia, symptomatic epilepsy microcephaly and strabismus.

Brain section was performed by Dr Erna Christensen. The brain weighed 600 grams following fixation. Its shape was normal, though the cerebrum was considerably smaller than normal. Microgyri were seen all over the convexity though not of uniform distribution. On the lower aspect of the right frontal lobe the gyri were flattened, presumably due to enlargement of the anterior horn. The leptomeninges were not thickened. The vessels showed no definite changes. The cerebellum was of normal size and had normal gyri. Frontal section revealed spongy brain tissue with networks of varying size. The degeneration was most pronounced on the convexity and in the anterior two-thirds of the cerebrum there was atrophy of the gyri in the parieto-occipital lobes, but no polyporencephaly was observed. The ventricles were severely enlarged. The cystic necrotic processes had invaded the insula and the lateral areas of the corpus striatum in both sides. In the area of the thalamus, at the level of the massa intermedius bilateral atrophy was present in the upper median portions in the form of yellowish necrotic processes. Yellowish discoloration was not observed elsewhere. The remaining areas of the basal ganglia were sclerotic, with blurred outlines. The aqueduct and the fourth ventricle were not enlarged. There was slight granulation in the ependyma on the walls of the lateral ventricles and possibly also in the fourth ventricle. The cerebellum, pons and medulla oblongata were macroscopically normal on the sectioned surfaces.

Pathological diagnosis: pronounced polyporencephaly due to cerebral anoxia.

No. 14 (26001/205/1955)

A girl born in hospital on March 8, 1955 to a 30 year old primipara following normal pregnancy. The delivery was normal. BW was 3800 g. No asphyxia. Admitted to the DPGe on the second day because of convulsion and suspected intracranial haemorrhage. The convulsion did not recur, but she remained rigid, trembling and with a high-pitched cry until the 10th day. There was a cephalhaematoma in the right side. The eye movements were nystagmoid, and ophthalmoscopy showed retinal haemorrhages. On discharge, 14 days later her condition was good, but follow-up was recommended.

Diagnosis: intracranial haemorrhage.

Re-examination at NPO of the RH at 3 months revealed spasticity in all four limbs, restlessness, tremor, sensitivity to noise and a squint. Head circumference was normal at this time, but at about 2 years of age it was just below average, and when last seen at well over four years, it was well below the normal limit. At 9 to 10 months she had episodes of jerking in the legs, which did not recur, however from her third month she was treated with phenobarbitone and mysoline. Her mental development was slow. At 4 years her speech comprehension was poor and she was able to make only a few sounds. Growth was good during the early months of life, but subsequently poor. Motor function was very defective; when seen last at four years she was unable to sit up alone.—There was no family history of cerebral disease.

Diagnoses: mental deficiency, spastic quadriplegia, microcephaly, strabismus.

No. 15 (26262/3/1955)

A girl, born at term in a private clinic on March 11, 1955, to a primipara, who in the first month of pregnancy had been operated on for corpus luteum cyst. Otherwise the pregnancy was normal. The prolonged delivery was stimulated by 13 or 14 injections because of lack of progress. The heart sound eventually became affected, and the infant was delivered by forceps. She was asphyxiated for an unknown length of time and was admitted to the DPGe during her second day of life because of convulsions and suspected intracranial haemorrhage. On admission she was rigid, restless and screaming, and during the second to fifth day she experienced numerous convulsions. There were also several episodes of harlequin colour change. The rigidity subsided within eight days. However, her condition was described as unsatisfactory at discharge after 26 days, though no particulars were given. The outlook was considered doubtful.

Diagnoses: intracranial haemorrhage, nystagmus, strabismus.

Her development was severely retarded. At 7 months diagnosis of spastic quadriplegia was made on O.P. examination at the DPGe. Subsequently she was treated at other hospitals. She achieved no motor function and had hardly any contact with her surroundings. She could smile and focus, however. Her hearing was thought to be impaired and she did not talk. She was very restless. At about 18 months she experienced two episodes of convulsions and from the age of two, or two-and-a-half she exhibited repeated seizures.

EEG at 1 year 7 months showed an atypical pattern with absence of activity in central-parietal and central tracings in sleep as well as waking record. Frontal and temporal tracings revealed spikes, more pronounced on the left side.

PEG at the same age disclosed excessive enlargement of the lateral ventricles, the left being larger than the right. No cortical air was seen.

Her growth was poor and she had to be fed by tube most of the time. At about 18 months she was put under SA and at about 2 years she was placed in an institution (Karensminde), where she died of bronchopneumonia some seven months later.

There was no family history of cerebral disease.

Diagnoses: mental deficiency, spastic quadriplegia, symptomatic epilepsy, microcephaly.

Brain section was performed by Dr. Erna Christensen. The weight of the fixed

brain was 350 g. The cerebrum had been completely destroyed leaving a wall of only a few millimetres thickness, and the basal ganglia, which were atrophic. Brownish necrotic processes were observed laterally in the corpus striatum, otherwise no haemorrhage was seen. The cerebellum and brain stem were macro-and microscopically normal.

Pathological diagnosis: polyporencephaly due to cerebral anoxia.

No. 16 (5535/205/1955)

A boy born at term in a private clinic on June 10, 1955 to a grossly overweight primipara, who had exhibited oedema during pregnancy Her blood pressure and urine were normal however The delivery was induced and prolonged, and was accomplished by forceps with axis traction. There was no record of asphyxia, but the infant was given oxygen and lobeline immediately after birth and was referred to the DPGs without delay On admission his condition was poor He suffered several cyanotic attacks during the first day He was restless, rigid and trembling, and there was grunting respiration. During the first few days there were repeated convulsions. His restlessness decreased after the fifth day but the rigidity and tremor lasted until the tenth day He was discharged on the 15th day in apparently good condition, but out patient follow-up was recommended.

Diagnoses: Intracranial haemorrhage, difficult birth.

He was readmitted when 2½ months old following vomiting and poor growth due to suspected pyloric stenosis. This diagnosis was not confirmed. He was markedly spastic, trembling, with a tendency to opisthotonus, and could neither focus nor smile. The diagnosis was spastic quadriplegia, suspected mental deficiency The prognosis was considered to be grave.

PEG at 4 months revealed generalized pronounced enlargement of the ventricular system.

From this time on he suffered frequent clonic seizures and was given anti-convulsant therapy with some benefit.

EEG performed at 5 months showed severe abnormalities with generalized synchronous spikes and spike waves.

Head circumference at 6 months was lower borderline normal, and later on was clearly below even this limit. Motor as well as mental development was extremely retarded. At the age of 9 months he came under the care of SA and later was admitted to an institution (Andersvænge), where he died at the age of 2 years and 3 months.

There was no family history of cerebral disease.

Diagnoses. mental deficiency spastic quadriplegia, symptomatic epilepsy microencephaly

Brain section revealed microcephaly and microgyri, polyporencephaly especially cortical internal hydrocephalus, due to cerebral anoxia. The weight of the fixed brain was 500 g.

No 17 (7116/205/1955)

A girl born at term in a private clinic on June 30, 1955 There was no record of age and parity of the mother nor of the pregnancy The delivery was prolonged and was stimulated by repeated injections. Forceps with axial traction was applied. The infant was asphyxiated for 30 minutes, in the course of which 1½ ml of coramine was given. She was immediately transferred to the DPGs in a desperate condition. flaccid, drowsy and showing no spontaneous movement. Subsequently she became restless, rigid and trembling. Over the first few days she sustained several cyanotic attacks with collapse. From the 8th day she recovered somewhat, however sucked and progressed poorly for 1½ months. At discharge, following 53 days' stay the outlook was considered doubtful.

Diagnosis: intracranial haemorrhage.

5 months later she was admitted to neurosurgical department (Bispebjerg Hospital). Following PEG studies, which revealed symmetrical enlargement of the ventricular system, diagnoses of cerebral atrophy following difficult birth, spastic quadriplegia, mental deficiency and microcephaly were made. She also suffered repeated clonic convulsions.

EEG was severely abnormal. No details are available, however

She was placed in a nursery where she died 1 / years old. Post mortem was not carried out.

No familial cases of cerebral disease were elicited.

No. 18 (7653/3/55)

A girl, born in a private clinic at term on July 7 1955, to a 37-year old multipara, following pregnancy complicated by permanent nausea. The delivery was uncomplicated, but very quick. However the infant had the cord around its neck and was asphyxiated for few minutes. Lobeline was given. Because of convulsions she was admitted to the DPGe during the first 24 hours of life, in extremely poor condition: flaccid, drowsy and cyanotic. She remained almost stuporous for the first week. Subsequently she became rigid. There were repeated cyanotic attacks during the first few days. Throughout the two months of her stay she suffered recurrent convulsions despite anti-convulsant therapy: the rigidity persisted and her growth was unsatisfactory

Diagnoses: *intracranial haemorrhage*, cerebral palsy *symptomatic epilepsy*

She was readmitted at 6 months of age because of continued convulsions.

EEG 1) at six months was severely abnormal with frequent bursts of spikes with rightsided preponderance.

Her development was severely retarded and her growth remained poor The previous diagnosis of spastic quadriplegia was supplemented by mental deficiency and microcephaly

Her later development was extremely slow in all respects and she continued to exhibit minor convulsions. She did not respond to noise and did not talk. At about 4 years she was admitted to the Dept. of Paediatrics of the RH.

EEG 2) at this time was again severely abnormal. Her sleep record as well as the waking record were characterized by spikes and spike waves of 2–3 per second, with changing laterality

PEG revealed moderate enlargement of the lateral ventricles. The third ventricle was large owing to agenesis of the corpus callosum. There was considerable cortical air

At about 4 years she was placed under the care of SA. She died 4 years 2 months old from bronchopneumonia.

Brain section by Dr Erna Christensen showed microencephaly and microgyri, predominantly in the cerebellum, dysplasia of the cerebrum due to perinatal anoxia, bilateral hydrocephalus with dysgenesis of the corpus callosum and the septum pellucidum. No anlage-abnormalities were seen, however, there were signs of partially arrested development during the perinatal period with degenerative changes in the form of gliosis, presumably due to anoxia.

There was no family history of cerebral disease.

No. 19 (442/3/1947)

A boy born at term in hospital on Aug. 21 1947 to an unmarried primipara following normal pregnancy Normal delivery no asphyxia. Admitted to the DPGe at 24 days because of convulsion on the previous day On admission the infant was febrile and trembling, and during the first three days of admission he had several seizures. Lumbar puncture was performed, the spinal fluid was straw-coloured, but otherwise normal. Jaundice, which had started on the second day of life, had subsided before admission. The temperature quickly fell to normal. There were no alterations of tone, but the eye movements were nystagmoid. The infant was discharged after 32 days in apparently good condition, though the nystagmus persisted.

Diagnosis: intracranial haemorrhage.

The maternal grandparents, who cared for the child, took him to a doctor at the age of one year as they considered that he was backward. He was unable to sit and was quiet and rather listless. Vision and hearing were felt to be normal. The somatic development was satisfactory and the neurological examination was normal (OP RH).

He could sit up alone by the time he was 2 years old and walk alone by 2½. His motor pattern appeared normal. Up to the age of 3 years he was very placid, but for a number of years subsequently became unmanageable and destructive. From the age of 6 he was no longer destructive, but ran around aimlessly and would not occupy himself. His fosterparent (maternal grandparents) had never really accepted the child, and the mother had gone abroad. When just over 3 years of age he was put under the care of SA and at about 5 years he was placed in an institution (Ebberødgård). There he was examined at the age of 10⁴/₁₂. His behaviour was as mentioned above. He did not talk and no contact could be made with him. Somatic development and neurological examination were normal.

There was no family history of cerebral disease. The father was said to have been very moody

Diagnoses: idiocy aphasia, previous motor retardation.

No. 20 (15527/3/1952)

A girl born before *term at home on Dec. 11 1952, to a 33-year old multipara* following an uncomplicated pregnancy and a normal delivery BW was 2300 g. No asphyxia. Sucked poorly for the first seven days at home and on the seventh day suffered a severe cyanotic attack, as a result of which she was given coramine and admitted to the DPGe. On admission she was moderately jaundiced there was, however no bloodgroup-incompatibility between mother and child, and the jaundice gradually subsided. On the day of admission and the next day several quite severe cyanotic attacks were observed, but were not repeated. A lumbar puncture was done. The spinal fluid was yellow but otherwise normal. There were no changes of tone or respiration. She was discharged after 29 days, in apparently good condition.

Diagnosis: sequelae of intracranial haemorrhage.

When she was about 2 months old her parents suspected that her head was larger than normal. This was confirmed at examination at the age of 3 months. At 4 months *she was admitted to the Dept. of Neurosurgery of the RH Ventriculography* was performed and revealed excessive enlargement of the ventricular system including the fourth ventricle, and a ventriculo-cisternotomy was carried out. Operation revealed a severe arachnoiditis.

Her motor development was negligible. She was never able to sit or stand and was generally helpless. No definite neurological signs were demonstrable. She was placed in an institution under the SA (Andersvænge) at 2 / years of age. She was placid smiled on contact, but she could not talk and displayed no other mental activity Her vision and hearing seemed normal. Head circumference was far above the upper normal limit (78 cm), but did not increase until shortly before the age of 3 when her conditions deteriorated. She died at the age of 3 years 1 month after four days high temperature and an episode of severe convulsions. At that time her head circumference was 86 cm.—In early life, probably within the first year there had been a period of recurrent brief convulsions with raising of the arms—which, however had ceased spontaneously before admission to Andersvænge (infantile spasm?).

No family history of cerebral disorder was reported.

Diagnoses. idiocy pronounced hydrocephalus, symptomatic epilepsy aphasia.

Brain section (Dr Erna Christensen) showed severe internal hydrocephalus due to an Arnold-Chiari syndrome, suppurative meningitis, most pronounced in the posterior fossa, occlusion of foramina Magendi et Luschka, incipient granular ependymitis. (The cerebrospinal fluid amounted to 4 1 litres).

No. 21 (13599/3/1953)

A boy born at term in hospital (RH) on Oct. 8, 1953. The mother was a multipara, she had been subject to oedema and vomiting during the pregnancy. The delivery was preceded by feeble labour for 10 days; it lasted for 50 hours and was stimulated several times. Otherwise the course was normal. BW was 4100 g. No asphyxia. During the first few days the infant was flaccid, but later became rigid and restless. On the 12th day he was transferred to the DPGe, still somewhat rigid, and making poor progress. Hydrocephalus was suspected, as it had been at the RH. He also had right-sided pes equino-varus. When discharged 18 days later he was still moderately rigid.

Diagnoses: sequelae of prolonged delivery, right-sided pes equino-varus.

The parents suspected delayed development shortly before the child was six months old, because of listlessness, lack of response and unsatisfactory growth. When 13 months old he was referred to the OP of the RH because of suspected hydrocephalus. His head circumference was obviously above the upper normal limit and he was severely retarded physically as well as mentally. He was transferred to the Dept. of Neurosurgery RH, where PEG was performed. This revealed enlargement of the lateral ventricles, more pronounced on the left side. The third ventricle was poorly filled, the fourth ventricle was in correct position. The radiological diagnosis was generalized cerebral atrophy—sequelae of birth trauma? Operation was not recommended. At the age of 18 months he was placed under the care of SA and shortly after admitted to an institution (Ebberødgård). He sat up alone at 2 years 9 months, walked at 3 years 9 months. His gait was affected by his foot deformity. Hand movements were normal. He was severely mentally defective; at the age of 3 years his DQ was 47 (according to Bühler Hetzer). He was placid and cheerful, glad of company, could play with simple toys. His head circumference was still above the upper normal limit, but had not increased further and the shape of his head was not markedly hydrocephalic. He had epicanthus and single horizontal palmar lines, but no other mongoloid features. His vision and hearing were felt to be normal, but he had a mild squint. He could say single words at about 5 years.

No family history of cerebral disease was elicited.

Diagnoses: imbecility, hydrocephalus, aphasia, strabismus, pes equino-varus.

No. 22 (20453/3/1954)

A boy born at term in a private clinic on Jan. 12, 1954, to a multipara, who had ptyalism and vomiting during the pregnancy. The delivery was induced due to weight loss. The course was uncomplicated and the infant was not asphyxiated. He was somewhat restless during the first 24 hours, subsequently flaccid, and sucked poorly. He was therefore admitted to the DPGe. on the 8th day. The flaccidity persisted and he continued to suck poorly but eventually his growth became normal. He was discharged after 13 days in apparently good condition.

Diagnosis: congenital debility.

The parents first suspected that something was wrong when at the age of 2–3 months he was very restless and flaccid, and he was re-admitted for observation at 3 months. His muscle tone was difficult to judge, as were his vision and hearing. The tentative diagnosis was Little's disease.

He was able to stand up with help at one year walked by the age of 2 years. He used his hands in normal way. His growth was poor during his first two years, but subsequently became normal. His mental development was retarded, though specific testing was never carried out. On examination, at the age of 3 years, his development was estimated to correspond to the age of 1½ years. His speech was much retarded. At follow-up, when aged 4½ years, he was able to say only single words. His hearing was much impaired. He was examined at the National Centre for the Deaf, on the last occasion at about 4½ years. The diagnosis was bilateral neurolabyrinthopathy, suspected aphasic disturbance. It was suggested that the peripheral

hearing loss was complicated by some other form of hearing defect of unknown aetiology He was given a hearing-aid, but would not use it. His head circumference had always been high borderline normal, hence a PEG was performed at the age of 18 months, which revealed a mild internal hydrocephalus. At the same age angiocardiography revealed an asymptomatic cardiac malformation in the form of an abnormal entrance of the inferior vena cava. On follow-up he appeared mentally retarded his development was estimated as that of a 2 year old. He made himself understood quite well by means of gestures. Though somewhat clumsy no definite neurological abnormalities could be found. His vision was normal. His head circumference was just below the upper limit of normal.

There was no family history of cerebral disease.

Diagnoses. mental deficiency hypacusis (neurolabyrinthopathy), suspected aphasia, motor retardation, mild hydrocephalus, (congenital heart disease).

No. 23 (18337/3/1954)

A boy born at home on Nov 19 1954 a little before term to a 33-year old primipara following a normal pregnancy The delivery was uncomplicated, BW .500 g. The infant was asphyxiated for 5 minutes, initially flaccid thereafter he became restless, rigid and sucked poorly For that reason he was admitted to the DPGo on the 12th day Here he remained restless, mildly rigid and sucked poorly He was discharged after 20 days.

Diagnoses: congenital debility suspected cerebral palsy

The father had epilepsy though had been seizure-free for two years at the time of the patient's birth. The mother had migraine.

At the age of 6 weeks the boy was readmitted because of poor growth. He was found to be slightly rigid, trembled when he cried, and sucked poorly The diagnosis was suspected cerebral palsy His growth soon after became normal.

He was able to sit up alone at 10 months and walk alone at 2 years, though his gait was unsteady At follow-up, when he was aged 4 years, he was still somewhat clumsy though he walked normally in spite of moderate knock knees and flat feet. Neurological examination was normal. His mental development was retarded his speech was severely defective, consisting of only a few words. However he seemed to have normal comprehension of speech and normal hearing. At 3 4 and 5 years he was seen at the State Institute for Speech Disorders with a view to speech therapy However each time he was felt to be too immature. Asphasia was suspected.—When about 5 ½ years old he was placed under the care of SA. At this time his mental development was estimated to equal that of a 3-year-old.

He was seen repeatedly at the NPO, RH, where, at the age of 18 months, a mild paraplegia was suspected. The diagnosis was later modified, since no abnormalities of muscle tone or reflexes were demonstrable.

Final diagnoses: mental deficiency aphasia, motor retardation.

No 24 (24248/3/1955)

A boy born at term at the RH on Feb. 2, 1955 to a 40-year-old primipara following a normal pregnancy The delivery was normal however the membranes had ruptured 4 days prior to delivery There was asphyxia for a few minutes. He was transferred within the first 24 hours to the DPGo suspected of hydrocephalus. During the first day of life he exhibited cyanotic attacks, rigidity and opisthotonus alternating with flaccidity The latter persisted for a few days the other symptoms regressed after the first day He was discharged after 20 days in apparently good condition No evidence of hydrocephalus was found, though the head, on admission, showed pronounced moulding.

Diagnosis: intracranial haemorrhage

The parents suspected that the child's development was retarded when at 18 months he was unable to walk and continued to be restless. He sat up at the usual age of

6 months. At 2 years, having just begun to walk, he was examined by two neurologists, one of whom felt that the patient was "spastic" while the other did not. On follow-up, at the age of 4, he was somewhat clumsy his gait rather broad-based and his running rather slow for his age: however, no abnormalities of muscle tone or reflexes were elicited. His hand movements were normal. He appeared somewhat mentally retarded and his speech was severely retarded consisting of only single words. His comprehension of speech was relatively good and he made himself understood by gestures. The somatic development was satisfactory. However his head circumference was clearly below the lower normal borderline.

At 4 years 3 months he was tested by a psychologist at the Dept. of Paediatrics of the RH, who found an IQ of 59 and the mental development compatible with his level of speech. On this occasion he was also seen by a speech therapist, who found lack of concentration and receptive weakness. At 5 years of age he was placed under SA.

When 2 years old he experienced an episode of pallor and unconsciousness, probably accompanied by flaccidity. Similar episodes occurred at the age of 4 and 4 years 2 months. He was very sensitive to noise.

An EEG done at 4 years 3 months was normal. Repeat EEG at 5 years 1 month showed normal waking pattern, during sleep a spike focus was seen in the left temporo-frontal tracing.

There was no family history of cerebral disease.

Diagnoses: mental deficiency, previous motor retardation, aphasia, symptomatic epilepsy, microcephaly.

No. 25 (7791/205/1955)

A boy born at home at term on July 7, 1955, to a multipara following normal pregnancy. The delivery was not prolonged, however was stimulated by injections and terminated by expulsion due to an abnormal heart sound. BW was 4500 g. The infant was asphyxiated for about 5 minutes. He was admitted to the DPGe on the second day with diagnosis of asphyxia and congenital heart disease following cyanotic attacks beginning on the first day of life. He was flaccid and restless and had several cyanotic attacks the next few days. From the third day onwards he was trembling and during the fourth to sixth day he had repeated convulsions. Thereafter the symptoms regressed and he was discharged on the 20th day in apparently good condition. No evidence of heart defect had been detected.

Diagnosis: intracranial haemorrhage.

The parents suspected retarded development when the boy was 6–7 months old. He sat up alone at 9 months, walked alone at 2 years. At follow-up, when he was about 3½ years old, his gait seemed somewhat slow and too broad-based for his age, and he was unable to run. Otherwise his motor pattern was normal and he failed to exhibit any change of muscle tone or reflexes. His height was 12 cm below average, but he was well-nourished and well-proportioned. However his head circumference was clearly below the lower normal borderline (48.5 cm). He had a convergent squint. His hearing and vision were felt to be within normal limits, but he was mentally retarded and conspicuously unresponsive. His mother complained that she never made visual contact with him. At home he was not interested in other people or toys and was very temperamental. His speech was characterized by reiterations. During his first year of life he had been seen at intervals at the OP clinic at the RH, but later appointments had not been kept. He was found to be retarded, but neurological examination was negative. At follow-up psychological examination was planned, but the parents were not interested. EEG was normal.

The diagnoses were mental deficiency, suspected autism, previous motor retardation, microcephaly, convergent strabismus.

At the age of 7 years he was seen again at the above clinic, as he had reached school age and his parents doubted that he could get on at a normal school. His

motor pattern was normal, but in stress-situations strange, stereotyped hand movements were observed. The neurological examination was normal. His development had been unsatisfactory. He showed lack of concentration and never played alone or with other children and had no real contact with anybody. He seemed to have great difficulty in orientation within as well as out of the home, and the mother felt that his vision was poor. His speech was quite good, but he was unable to carry on a conversation. He would often repeat questions when asked and he still reiterated words and sentences over and over. His hearing was thought to be good. Eye examination was negative apart from a squint. EEG was still normal. Psychological tests revealed an IQ (Binet) of 48. The distribution of correct answers indicated an organic factor with a predominance of perceptual disturbances. He was placed under the SA.

No family history of cerebral disease was elicited.

No. 26 (708/3/1948)

A girl born in a private clinic at term on Nov. 6, 1948, to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by injections; the presentation was anterior vertex. Forceps were used. The infant was asphyxiated for about five minutes, at first was flaccid and subsequently restless. On the second day she was admitted to the DPGe because of convulsions, the suspected diagnosis being rupture of the cerebellar tentorium. On admission she was restless and rigid during the second to fourth day there were repeated convulsions. The convulsions as well as the increased muscle tone were bilaterally equal. A transitory right sided facial nerve palsy was observed. The symptoms decreased and she was discharged after 16 days in apparently good condition. The diagnosis at discharge was intracranial haemorrhage.

When the child was about 4 months old her parents realized that she did not use the limbs on her left side to the same extent as those on the right. At 8 months she was admitted to the Dept. of Paediatrics at the RH where a diagnosis of left-sided spastic hemiplegia was made. She sat alone at 6 months, walked alone at 2 years. Mental development was normal. At follow-up, at well over 10 years of age, she exhibited a pronounced left-sided spastic paresis with atrophy of the limbs of the left side. Her somatic development otherwise was satisfactory. Mentally she appeared perfectly normal and had been able to attend a normal school. Her speech was normal.

There was no family history of cerebral disease.

Diagnosis: left-sided spastic hemiplegia.

No. 27 (12392/3/1951)

A girl born in hospital at term on Oct. 17, 1951 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by repeated injections owing to weak labour. Kielland's forceps were used. The BW was 4800 g. No asphyxia was reported. She was rather restless and sucked poorly. On the ninth day she suffered cyanotic attacks and convulsions and was admitted to the DPGe with a suspected intracranial lesion or congenital malformation. The cyanotic attacks and convulsions recurred from the ninth to the eleventh day; she was rigid and trembling. The symptoms abated and she was discharged after 15 days in apparently good condition.

The diagnosis, intracranial haemorrhage.

She walked alone at 18 months, but unsteadily and on her toes. At about 2 ½ years she was seen by a neuropaediatrician at the Orthopaedic Hospital, who made a diagnosis of mild spastic paraplegia. Her head circumference was obviously above the upper normal limit, and hydrocephalus was suspected. Her speech was normal, her mental development was also thought to be normal.

During her early years the patient experienced four episodes of chill, sweating and vomiting followed by sleep. At the age of 3 years she had an attack of unconsciousness, was started on anticonvulsant drugs and shortly thereafter admitted

to children's hospital (Queen Louise's Hospital). PEG was performed, revealing moderate dilatation of the left lateral ventricle, while the right was normal. When she had been seizure-free for a period of three years, the treatment was discontinued, the seizures recurred, however and the anticonvulsant therapy was reinstituted.

The following EEG-records were made: 1) at 3 years: no definite abnormalities, 2) at 3½ years: abnormal, with mild, generalized dysrhythmia in the form of slow activity for the age; spikes in the left hemisphere, 3) at 4 years: periods of normal activity less slow potentials, spikes persisting, 4) at 6 years 9 months. less abnormal.

At follow-up, hen 6½ years old, the patient appeared mentally normal. She had squint and used glasses. *Her speech* was normal; so were her hand movements. The legs were mildly spastic. Her head circumference was clearly above the upper normal limit.

There was no family history of cerebral disease.

Diagnoses: mild spastic paraplegia, mild internal hydrocephalus, symptomatic epilepsy strabismus.

No. 28 (7736/3/1953)

A boy born at term in private clinic on July 29 1953 to a primipara following normal pregnancy The delivery was stimulated by repeated injections; cephalo-pelvic disproportion was suspected. Forceps with axial traction were applied. Asphyxia was not observed. The infant was transferred to the DPGs shortly after delivery because of cyanotic attacks and a haematoma in the right parietal region. He was restless, had episodes of apnoea and one convulsion within the first 24 hours. The next days he was restless, but otherwise normal. A skull fracture was demonstrated. He was discharged on the 23rd day in apparently good condition, follow-up was recommended, however

Diagnoses: skull fracture due to birth injury suspected intracranial haemorrhage.

The parents suspected that something was wrong, when at 3–4 months the child did not smile and appeared flaccid. He was therefore readmitted at 6 months and was found to be physically retarded and rather flaccid. PEG revealed no abnormalities.

The diagnosis: mild case of Little's disease.

At the age of 7 months he was examined by neuropaediatrician at the Orthopaedic Hospital. No alteration of tone was demonstrable, but a mild disturbance of coordination was suspected. The diagnosis was cerebral palsy?, sequelae of intracranial haemorrhage? The prognosis was considered excellent.

His motor development was very slow during the first two years of life. At about 2 years, however accelerated, he learned, in rapid sequence, sitting and walking, but his balance was poor and he had *difficulty* in controlling head movements. His mental development was considered satisfactory At about 2 years of age he said single words and at three he was able to form sentences, though with faulty pronounciation. At the age of 4 years his hearing was found to be defective. Focusing had always been difficult; his vision was thought to be normal, however At follow-up, at the age of 5 his motor pattern was still characterized by defective coordination, his gait was unsteady and he was unable to run. Fine movements of the fingers were impaired. The muscle tone was variable, often slightly increased. The somatic development otherwise was satisfactory His speech was characterized by faulty articulation and mild stammering. He was able to focus briefly and had mild convergent strabismus. Mentally he appeared essentially normal.

Familial cases: none.

Diagnoses: athetosis, impaired hearing, impaired articulation, convergent strabismus.

No. 29 (4430 3/1954)

A boy born at term at home on May 29 1954, to primipara following a normal pregnancy The delivery was prolonged, but apparently normal. BW was 5210 g. The infant was asphyxiated for few minutes, for which artificial respiration as well as nikethamide and alternating hot and cold baths are given. He was immediately ad-

motor pattern was normal, but in stress-situations strange, stereotyped hand movements were observed. The neurological examination was normal. His development had been unsatisfactory. He showed lack of concentration and never played alone or with other children and had no real contact with anybody. He seemed to have great difficulty in orientation within as well as out of the home, and the mother felt that his vision was poor. His speech was quite good, but he was unable to carry on a conversation. He would often repeat questions when asked and he still reiterated words and sentences over and over. His hearing was thought to be good. Eye examination was negative apart from a squint. EEG was still normal. Psychological tests revealed an IQ (Binet) of 48. The distribution of correct answers indicated an organic factor with a predominance of perceptual disturbances. He was placed under the SA.

No family history of cerebral disease was elicited.

No 26 (708/3/1948)

A girl born in a private clinic at term on Nov. 6, 1948 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by injections; the presentation was anterior vertex. Forceps were used. The infant was asphyxiated for about five minutes, at first was flaccid and subsequently restless. On the second day she was admitted to the DPGo because of convulsions, the suspected diagnosis being rupture of the cerebellar tentorium. On admission she was restless and rigid during the second to fourth day there were repeated convulsions. The convulsions as well as the increased muscle tone were bilaterally equal. A transitory right sided facial nerve palsy was observed. The symptoms decreased and she was discharged after 16 days in apparently good condition. The diagnosis at discharge was intracranial haemorrhage.

When the child was about 4 months old her parents realized that she did not use the limbs on her left side to the same extent as those on the right. At 8 months she was admitted to the Dept. of Paediatrics at the RH where a diagnosis of left sided spastic hemiplegia was made. She sat alone at 6 months, walked alone at 2 years. Mental development was normal. At follow up, at well over 10 years of age, she exhibited a pronounced left sided spastic paresis with atrophy of the limbs of the left side. Her somatic development otherwise was satisfactory. Mentally she appeared perfectly normal and had been able to attend a normal school. Her speech was normal.

There was no family history of cerebral disease.

Diagnosis: left-sided spastic hemiplegia.

No 27 (12392/3/1951)

A girl born in hospital at term on Oct. 17, 1951 to a primipara following a normal pregnancy. The delivery was prolonged and stimulated by repeated injections owing to weak labour. Kielland's forceps were used. The BW was 4800 g. No asphyxia was reported. She was rather restless and sucked poorly. On the ninth day she suffered cyanotic attacks and convulsions and was admitted to the DPGo with a suspected intracranial lesion or congenital malformation. The cyanotic attacks and convulsions recurred from the ninth to the eleventh day: she was rigid and trembling. The symptoms abated and she was discharged after 15 days in apparently good condition.

The diagnosis: intracranial haemorrhage.

She walked alone at 18 months, but unsteadily and on her toes. At about 2 ½ years she was seen by a neuropaediatrician at the Orthopaedic Hospital, who made a diagnosis of mild spastic paraplegia. Her head circumference was obviously above the upper normal limit, and hydrocephalus was suspected. Her speech was normal, her mental development was also thought to be normal.

During her early years the patient experienced four episodes of chill, sweating and vomiting followed by sleep. At the age of 3 years she had an attack of unconsciousness, was started on anticonvulsant drugs and shortly thereafter admitted

Pethidine was also given twice. The *infant* was asphyxiated for a few minutes. She was admitted to the DPGe within the first 24 hours because of grunting respiration, th diagnosis of suspected intracranial haemorrhage. She recovered rapidly and was discharged 2 days later.

Diagnosis: congenital debility

She sat alone at 8 months and walked alone at 16 months. There were no motor problems. Her mental development was satisfactory. She *talked intelligibly* at 2 years, and her hearing was normal.

She had no convulsions, though within the *first three years of life* she suffered some ten brief spells of unconsciousness.

She as followed-up at about 5½ years of age. *Clinical and neurological* examination was normal except for a slight, non-familial divergent strabismus.

An EEG carried out when she was under 6 years old was mildly abnormal with dominant frequency of 8 per second and a few small spikes in the right frontal region. During photic stimulation small spikes were also seen in right parietal region. Hyperventilation did not precipitate specific changes. During sleep small spikes on the right side were again seen, though less pronounced. The record was indicative of epilepsy

Diagnosis: fainting spells in the past, suspected epilepsy divergent strabismus.

No. 32 (620/3/1948)

A boy born at term at home on Oct. 10, 1948, to multipara, *following normal* pregnancy The membranes were thought to have ruptured one month prior to delivery hich was stimulated by injections. Morphia was not given. The infant was not asphyxiated, but was admitted to the DPGe during the first 24 hours because of cyanotic attacks. On admission he was cold, somewhat flaccid, and respiration was grunting. H recovered quickly however he sucked poorly for the first five days. This feature improved somewhat, but his growth was unsatisfactory throughout the first month. Otherwise his condition was normal, and he was discharged after 35 days in apparently good condition. Follow-up was recommended.

Diagnosis: congenital debility

His subsequent growth and motor development were normal. He walked alone at one year. His visual acuity was somewhat diminished due to left-sided cataract (familial). He talked at 18 months. His hearing was normal.

At the age of 4 years he was admitted to Blegdamshospitalet with a diagnosis of sequelae of measles and meningismus. He was treated with penicillin and discharged after week. The spinal fluid was normal.

His mental development had been fairly normal. H started school at the usual time, but had to repeat the second grade. Subsequently he did well. He had alway been hyperactive and aggressive, and his attention span was short. He did not get on well with his companions or older siblings.

There was no history of convulsions, but nocturnal enuresis was present until the age of 10 years at least.

At follow-up, at the age of 10 years, his physical development was in line with his age. H was somewhat obese. His mental development was also compatible with his age, but *during the examination he appeared rather restless. The* neurological examination was normal. An EEG was performed, *revealing* severe dysrhythmia with a number of generalized synchronous paroxysms *of low frequency* (3–4 per second) and spikes, with preponderance in the frontal-temporal tracing.

One year after this examination the patient was *reported to have suffered two* episodes of unconsciousness, during which he banged his head on the floor. Convulsions were not observed. He was given antiepileptic drugs *and subsequently followed-up* at the NPO at the RH. During the next four years he exhibited recurrent fainting spells at varying intervals. Difficulty in concentration and with his behaviour at school persisted, and later on he had trouble keeping job. EEG improved quickly and

mitted to the DPGe with a diagnosis of asphyxia. His condition was poor he was found to be weak, drowsy flaccid with peripheral cyanosis. Later he trembled and jerked, and this persisted to some extent on discharge 19 days later His growth was poor during the first two weeks, after which it improved.

Diagnosis: sequelae of difficult delivery

He was seen as an outpatient at the age of one month, at which time his growth was satisfactory he smiled and focused, but he had a mild squint he seemed to move his limbs normally but was still somewhat trembling and jerking. The patient was not followed-up, but his condition has been described in a report from the Orthopaedic Hospital at Arhus, where he had been seen because of a diagnosis of mild spastic paraplegia since the age of three years. His motor development had not been retarded he started to walk at 13 months; his gait had however been impaired by poor balance. His upper limbs had always appeared normal Earlier examinations had revealed a mild increase in muscle tone and reflexes in the lower limbs and a bilateral Babinski reflex. These findings became less pronounced over the years, and at six his gait was essentially normal His mental and somatic development as well as his speech had been satisfactory at all times.

There was no family history of cerebral disease.

Diagnoses: mild spastic paraplegia, strabismus.

No 30 (757/3/1952)

A girl born at home at term on April 14 1952, to a multipara following an uncomplicated pregnancy The otherwise normal delivery was stimulated by injections. No asphyxia was reported but coramine was given. Shortly after birth she was admitted to the DPGe with a diagnosis of congenital heart disease. On admission she was almost moribund cyanosed and flaccid with laboured respiration however she recovered within the first 24 hours and was discharged 4 days later in apparently good condition. There were no signs of heart defect.

Diagnosis: congenital debility

Information on subsequent development was unobtainable. After repeated requests she appeared at the follow-up accompanied by her grandmother who did not know anything about her past history

A discharge summary from the Dept. of Neurology at the RH where the child had been seen as an out patient, revealed that, since the age of 18 months, the child had exhibited episodes of flaccidity drowsiness, upward movements of the eyes and cyanosis of the lips lasting for about one minute and followed by deep sleep. The frequency of these episodes was not recorded. She was first examined at the age of 5 years because of these attacks. EEG was moderately abnormal and indicative of epilepsy with large spikes posteriorly towards the midline. Anticonvulsant therapy was instituted the frequency of the attacks diminished, their type changed, and one year later was described as psychomotor epilepsy The last EEG at the age of 6¹/₄ was still markedly abnormal the abnormalities were generalized, but with a preponderance to the left, however The diagnosis was epilepsy suspected atrophic encephalopathy due to neonatal anoxia.—She had nocturnal enuresis. Neither epilepsy nor enuresis were familial. She was said to be hyperactive, and it was felt that she would not be ready for school until the age of 8.

At follow-up, when the patient was well over 6 /₄ years, the only abnormal finding was a convergent squint. Physical development was in line with her age and she appeared sensible, intellectually possibly low borderline for her age. Her speech and motor pattern were normal. Neurological examination was normal, and there were no signs of heart disease.

Diagnoses: epilepsy mental retardation? nocturnal enuresis, convergent strabismus.

No 31 (11172/3/1953)

A girl born at term in a private clinic on Sept. 17 1953 to a primipara following a normal pregnancy The delivery was prolonged and stimulated by repeated injections.

fully on his own. When addressed in a loud voice, he could be brought out of the attacks. At 18 months of age he was readmitted to the DPGs following a generalized clonic seizure of a few minutes' duration, associated with fever. The examination was normal, except for a rash.

Diagnoses: exanthema subitum, febrile convulsions.

An EEG was recorded at age two years, showing no abnormalities. He was seen at follow-up at the age of 3, at which time he had developed according to his age, physically as well as mentally. The neurological examination was normal.

Diagnoses: febrile convulsions, suspected epilepsy.

No. 35 (15152/3/1952)

A boy born at a private clinic, shortly before term, on Dec. 9, 1952, to a primipara, following a normal pregnancy. The delivery was prolonged. There is no record of the use of labour stimulation or morphia. Apart from breech presentation the delivery was uncomplicated. BW was 2400 g. The infant was not asphyxiated and was essentially normal for the first two days. However on the third day he developed cyanotic attacks and convulsions. He was admitted to the DPGs and on that day had one more seizure. He was restless and trembling for the first three days, but exhibited no symptoms during the rest of his stay and was discharged after 21 days in apparently good condition.

Diagnosis: sequelae of intracranial haemorrhage?

His growth was poor during the first year of life, then improved, even though he was somewhat undersized. His motor development was slow; he could not sit up until the age of 15 months or walk until about 20 months. At 8 months he was readmitted to the DPGs where encephalopathy and spasticity were suspected due to delayed development. Because of strabismus and nystagmus he was transferred to the Dept. of Ophthalmology. Ophthalmoscopy revealed no abnormalities. However it gradually became evident that the visual acuity was poor in both eyes, mainly in the left side. He underwent surgery for his squint at the age of 2 years and the following year was provided with glasses.

His pattern of movement was very unsteady to begin with, but improved considerably after he began to wear glasses. He was left-handed (not familial). From the age of 2–4 years he had two episodes of convulsion precipitated by temper tantrums. Until the age of 5 he would frequently grind his teeth at night. His mental development was satisfactory with no behaviour disorders. It was anticipated that he would be ready for school at the usual time. His hearing was normal and he talked by the time he was 2 years old.

He was well over 6 years old at the time of follow-up. His height was 7 cm below average; however he was well-proportioned and well nourished. His mental development appeared to match his age. His speech was normal. He wore glasses and had a patch over the left eye. With the use of glasses his motor pattern including fine co-ordinated movements was normal. Without glasses there was unsteadiness and there was obvious impairment of vision in both eyes. He preferred to use his left hand, though he had no trouble using his right hand. No neurological abnormalities were seen.

EEG at 7 years 3 months was normal.

Diagnoses: previous motor retardation, incipient amblyopia, convergent strabismus, breath-holding spells, previous poor growth.

No. 36 (178/3/1946)

A boy born at a private clinic before term on June 10, 1946 to a 27-year-old multipara following a normal pregnancy. The delivery was uncomplicated and not stimulated, no morphia was given. BW was 2150 g. The infant was cyanosed, but not asphyxiated at birth. Since he sucked poorly and had cyanotic attacks in association with feeding he was transferred to the DPGs aged one week. On admission he was jaundiced, but jaundice subsided within a few days, and he presented no other abnormal features

during the following four years the records were normal or only mildly abnormal; during the next two years they remained quite normal. There were no convulsions during this period. The antiepileptic drugs were therefore discontinued, and he remained seizure free as far as information is available i.e. for the next 6 months.

In 1960 at the age of 12, he was examined by a psychologist, who reported that the boy was normal to bright, but had difficulty meeting the demands made by himself and by others because of lack of development of the finer cerebral functions in relation to language an inability to put his thoughts together to take in and comprehend did not match his technical reading ability and the extent of his vocabulary. These features in a boy with epileptic symptoms would be regarded as manifestations of organic immaturity of the mild receptive-aphasia type.

Diagnoses: symptomatic epilepsy behaviour difficulties, enuresis, cataract of the left eye (familial)

No 33 (23947/205/1955)

A boy born in a private clinic at term on Feb 9 1955 to a primipara following a normal pregnancy Delivery was uncomplicated, not induced and morphia was not given The infant was not asphyxiated and exhibited no symptoms during the first days apart from some flaccidity On the fourth day he developed harlequin colour change and sucked poorly and he was admitted to the DPGe with a diagnosis of asphyxia. On admission he was flaccid and cold. The next day he had 2 episodes of left-sided convulsions, however recovered within a few days and had no further seizures. On the 13th day he was discharged in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth was normal. Motor development was good, though he could not sit up until he was 8 months or walk until 16 months. His motor pattern was normal however he was left handed (non-familial). His mental development was satisfactory and he presented no behaviour problems. There was a squint, but his vision was felt to be normal. His hearing and speech were also normal From the age of 13 months onwards he sustained 8 to 10 episodes of generalized clonic convulsions, all associated with fever The length of the episodes increased from between 5 and 10 to 45 minutes and were followed by sleep. The last episode occurred at the age of 3 years. No treatment was given. Familial history of convulsions was not reported.

At follow up he was 3 years 9 months old. Physical and mental development were in line with his age The neurological examination was normal. He preferred using his left hand, but was able to use his right hand well (i e. when eating). There was an intermittent squint.

EEG was normal.

Diagnoses: febrile convulsions, suspected epilepsy convergent squint, left handedness.

No 34 (20598/55)

A boy born at term in a private clinic on Dec. 13, 1955 to a primipara, following a normal pregnancy The delivery was uncomplicated and not induced. Pethidine was given once. The infant had the cord around the neck once, but was not asphyxiated. Because of cyanotic attacks he was admitted to the DPGe within the first 24 hours, suspected of a congenital heart disease and aspiration to the lungs. On admission his respiration was grunting, and he exhibited repeated cyanotic attacks during the first day His respiration was quickly corrected, and no abnormal features were apparent for the rest of his five days stay The examination revealed no evidence of heart disease.

Diagnosis: congenital debility

His growth and development were normal. He walked alone by one year and talked before he was two. His vision and hearing were normal so was his behavioural pattern. From the age of one year he exhibited daily episodes of drowsiness accompanied by staring and jerking of the arms, most frequent when he was playing peace-

Diagnosis: behaviour disorder convergent strabismus, amblyopia of the right eye, impaired hearing of the right ear (postinfectious), speech retardation, previous dysplasia.

No. 38 (23/3/1946)

A girl born in a private clinic before term on April 10, 1946, to a 29-year-old multipara following an uncomplicated pregnancy. The delivery was normal, no labour stimulation or morphia were given. BW was 1440 g. The infant was asphyxiated for 10 minutes and was given oxygen and artifical respiration and was transferred to the DPGs. During the first few days she suffered repeated cyanotic attacks, but was other wise normal apart from poor growth. She stayed in hospital for 12 days and was discharged in apparently good condition.

Diagnosis: prematurity congenital debility

Her growth was slow for the first 6 months, then improved. The motor development was rather slow: she did not sit up until rather late and did not walk until 22 months. Her motor pattern was normal. At a little over 2 years squint was noted, which was treated surgically at the age of 5. The mental development was satisfactory. However the parents recognized that something was wrong when at 4 or 5 years she still did not speak properly. At 6½ year she entered the State Institute for Speech Disorders, where a hearing loss, mainly of high frequencies, was revealed. She had trouble with her articulation of consonant combinations. A year later she started in a special class for children with hearing and speech defects at municipal school; she did fairly well and her speech improved. There was no change in her deafness. She got on quite well with other children, even though she was rather introvert and sensitive.

There was no family history of hearing loss.

At follow-up, aged 12, she was physically developed according to her age. Neurological examination and EEG-record were normal. She appeared mentally normal during the examination. She still had slight trouble with the pronounciation f, s, t, k and g.

Diagnosis: hearing defect, dysphasia, operated squint, previous poor growth, previous retardation of motor development.

No. 39 (161/2/1947)

A boy born at home before term on May 9 1947 to a 36-year-old primipara following an uncomplicated pregnancy. The delivery was normal. Labour stimulation was not applied, but one analgesic injection was given. BW was 1350 g. The infant was asphyxiated for a few minutes and was immediately admitted to the obstetric dept. of the RH. 13 days old he was transferred to the DPGs. His condition was quite good during the first few days of life, but after the fourth day he had to have oxygen intermittently due to cyanotic attacks. From the 24th day he was free from attacks. No other symptoms were observed. His growth was poor for the first two weeks, then improved. He stayed in hospital for 58 days and was discharged in apparently good condition.

Diagnosis: prematurity congenital debility

Subsequently his growth and development were satisfactory. He walked alone at 15 months and his motor pattern was normal. He began to talk rather late: at 3–4 years he said only single words, and when, at 6 years, he still did not talk properly he was given speech therapy for one year. He started school at the usual time. At school he had to have special lessons in reading for one year and he was referred to the National Centre for the Deaf. The examination revealed bilateral nerve deafness, due to premature birth. His hearing loss affected only high frequencies. He was given hearing aid, which he used at school. There was family history of deafness.

He offered no behaviour problems.

On follow-up examination, at 11 years, he was found to be normally developed,

apart from poor growth for the following 2 months. He was discharged after 152 days in apparently good condition.

Diagnosis: congenital debility

His development had been essentially normal. He walked rather late (18 months); however his motor pattern was quite normal. He started to talk before he was 2 years old, but did not speak properly until he was well over 6. He was therefore given speech therapy and within 3 months his speech was normal. Hearing and vision was normal. His mental development as regards learning was satisfactory. He started school at the usual time and did will. IQ (Binet) at 6 years was 114. His behaviour was characterized by restlessness, a violent temper and lack of concentration, for which reason he was admitted to a children's hospital (Queen Louise's Hospital) at the age of 6 and 8 years. The diagnoses were neurosis, environmental stress and dysphasia. The history revealed a good deal of "sibling jealousy" but otherwise no real precipitating environmental factors. EEG showed mild generalized dysrhythmia. The dominant frequency was 7–9 per sec. Both occipital and central leads showed at several points single potentials of 4–5/sec. During hyperventilation a strong build up of slow potentials was seen: the record soon became normal, however.—He had never exhibited any epileptic manifestations and no special treatment was given. His behaviour difficulties gradually subsided. Nocturnal enuresis was present until the age of 9 years.

There was no family history of enuresis, speech defect or epilepsy.

At follow-up, when he was about 12 years old, the boy was found to be somatically and mentally developed in line with his age. There were no complaints of behaviour problems, and on examination he appeared placid and sensible. The neurological examination was normal.

Diagnoses: behaviour disorder, cerebral dysrhythmia, previous dysphasia.

No. 37 (253/3/1950)

A boy born in hospital (St. Lukas Stiftelsen) before term on June 7, 1950, to a 39-year old multipara, following a normal pregnancy, during which she had felt very tired. The delivery was very quick. No drugs were given. BW was 2000 g. Asphyxia is not reported, though nikethamide was administered. The infant was immediately transferred to the DPGo with a diagnosis of prematurity. He was rather flaccid on admission and sustained cyanotic attacks during the first 24 hours. His growth was unsatisfactory for the first two weeks, then improved, and his condition was essentially normal when he was discharged after 33 days.

Diagnoses: prematurity, congenital debility

Growth was unsatisfactory for the first 6 years of life. During those years he suffered repeated infections of the upper respiratory tract. Following adeno-tonsillectomy at the age of 6 the infections ceased and his growth improved. His motor development was good: he sat up at 7 months and walked at one year; the motor pattern was normal. During his early years his hearing was thought to be normal. At the age of 7 a right-sided hearing loss was recognized, affecting high frequency sounds only and possibly caused by the previous middle ear infections. He had a convergent strabismus and was given glasses and an occlusive eyepatch. Visual acuity in the right eye was found to be diminished. His speech was retarded: he began saying single words at the age of 2. He stammered until the age of 4–5 and even after the age of 5–6 years his speech was only fair, with imperfect articulation of certain consonants.

His mental development was fair. However, his behaviour was characterized by restlessness and aggression. At the age of one and again at 2 years he was admitted to the DPGo with a diagnosis of neurosis, which was ascribed to environmental factors. He started school at 7 and did well.

At follow-up he was 8 years old, of about medium height, and obese. He had a convergent squint and wore glasses. His mental development was felt to be according to age, though possibly low borderline. His speech was normal. The neurological examination was normal. EEG was normal.

revealed aphasia, mainly of the expressive type. His intelligence could not be assessed exactly. He was placed in a group of patients with perceptive deafness and aphasia, where he made satisfactory progress after initial serious difficulties of adjustment. At the age of 8 he was again psychologically tested. His I. A. was found, with reservation, to equal 6½ years. The evaluation of his hearing had also been difficult. At the age of 8½ audiometry carried out at the National Hearing Centre revealed normal hearing. He was, nevertheless, provided with a hearing-aid, which it was anticipated would improve comprehension. As this was not the case, the hearing-aid was abandoned after 6 months. Following two years of therapy at the Institute for Speech Disorders he was transferred to the Institute for Dyslectics, which he attended at least until the autumn of 1966. He had great difficulties in talking as well as reading, though he worked hard and enjoyed the training.

His behaviour was unsatisfactory though less so than previously: he was extremely sensitive and irritable with other children. He had nocturnal enuresis until age 6. (Not familial).

He was 8½ years old at follow-up. Somatically he had developed in line with his age, his motor pattern was normal. Neurological examination was normal. Mentally he appeared babyish and clinging. His speech was defective and his articulation was poor. His comprehension of language was felt to be much improved. An EEG was recommended, but he did not attend at the appointed time.

Diagnosis: Aphasia, mainly expressive; mental retardation, previous motor retardation, previous enuresis, previous poor growth.

No. 42 (1523/3/1951)

A boy born at term on March 11, 1951, to a 32-year-old multipara following normal pregnancy. Delivery took place in a private clinic and was induced for unknown reasons. During the delivery, which was otherwise normal, morphia was given. The infant exhibited asphyxia for a few minutes, during which artificial respiration and coramine 0.4 ml were given. Within the first 24 hours the infant was referred to the DPGs with a diagnosis of prematurity. On admission his respiration was grunting; otherwise his condition was normal. Oxygen was given intermittently for the first six days. During the first 5 days he exhibited cyanotic attacks whenever gradual discontinuation of oxygen was attempted. After a few days his breathing became normal. After the 5th day he appeared normal except for poor growth, which persisted for two weeks. He was discharged after 23 days in apparently good condition.

Diagnosis: congenital debility.

His later growth was good, his physical and mental development were normal apart from marked restlessness and sensitivity to noise, mainly in the first 2 years. His vision and hearing were felt to be normal. He first began to talk at about 3 years of age, he said a few single words only and did not form sentences until the age of 5–6 years. He had mispronounciations of certain consonants, which did not justify speech therapy.

At follow-up when he was 7 years old, he was found to have developed in line with his age physically as well as mentally. He appeared placid during the examination. There was mispronounciation of h and r. Neurological examination was normal. He was referred for EEG, which was, however, postponed until he was 8½ years old and showed a normal record. At this time he had started school, he did well, and his speech was normal.

Diagnoses: mild dysphasia, previous hyperactivity.

No. 43 (9900 3 1952)

A boy born in hospital (St. Lukas Stiftelsen) at term on Sept. 16, 1952, to a primipara of 30 years. The delivery was prolonged, stimulating injections were given and forceps were applied. There is no record of morphia. BW 4000 g. The infant was not asphyxiated, though was rather flaccid at birth and subsequently restless. On the

mentally as well as somatically The neurological examination was negative. EEG was normal. There were a few mispronounciations—he had difficulty with t and k.—One year later speech therapy was repeated with good results. His progress at school was excellent.

Diagnoses: hearing defect, dysphasia.

No. 40 (1126/3/1949)

A boy born in hospital (Diakonissestiftelsen) at term on Feb. 10, 1949 to a 33-year-old primipara following an uncomplicated pregnancy The delivery was prolonged. Labour stimulating drugs were given no information available about morphia. Forceps were used No record of asphyxia. The infant was flaccid and sucked poorly and on the 13th day after developing a fever was transferred to the DPGe with suspected pneumonia. There his respiration was found to be normal, and examination of the lungs showed no abnormalities. The fever subsided within 3 days, he was still somewhat flaccid and sucked poorly during the following week, but then improved He was discharged 14 days after admission in apparently good condition.

Diagnosis. intracranial haemorrhage.

His later growth was normal. So was his motor development, although he did not walk until he was 18 months. His mental development was good he started school at the usual time and did well. He presented no behavioural problems. There was enuresis until the 7th year (not familial). He began to talk at the "usual" time, but with a few mispronounciations, mainly of b g and d. From the age of four impaired hearing was suspected. At 7 years he was taken to the Hearing Centre at Odense, where the diagnosis was bilateral congenital neurolabyrinthopathy (birth injury), high tone loss. He was given a hearing-aid, which he used with great benefit. On follow-up examination at the Hearing Centre one year later the findings were unchanged on the left side, but audiometry revealed progression of the defect on the right side.—There were no cases of deafness or speech defect in the family

At follow-up the child, now well over 10 years old, was found to be normally developed, mentally as well as physically The neurological examination was normal, the speech was normal. He still used a hearing-aid. EEG was not performed.

Diagnoses: bilateral congenital neurolabyrinthopathy previous mild dysphasia, previous enuresis.

No. 41 (91/3/1950)

A boy born at home at term on April 24 1950, to a 31 year-old multipara following a normal pregnancy There is no record of delivery complications or the use of morphia. Labour stimulating injections were given. Asphyxia is not mentioned. The infant was admitted to the DPGe on the first day because of cyanotic attacks. On admission he was rigid and somewhat trembling. No cyanosis was observed after the first day The rigidity subsided after a few days he improved and was discharged after 8 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth was poor for the first 6 months, then improved. His motor development was at first retarded—he could not sit up until one year old, but walked at 15 months, and his motor pattern was normal. At 3 years of age he was referred to the Finsen Institute suspected of retarded mental development. However because of poor co-operation and a pronounced speech defect his intelligence could not be assessed. This was also true half a year later when he was admitted to the DPGe because of pneumonia. His speech was still defective, he said only single and imperfectly articulated words. However he did seem to have a better comprehension of spoken words. He received no special speech training and, in spite of earlier referral, was not tested until 7 years of age, when he was seen by a school psychologist. Proper testing was again impossible· he was, however assessed as backward or feebleminded, and referral to the Institute for Speech Disorders was recommended. The examination

mission he was flaccid and cyanosed and his respiration was grunting. Cyanotic attacks are limited to the first 24 hours and respiration and muscle tone were restored to normal within few days. Thereafter he exhibited no symptoms and was discharged after 14 days in apparently good condition.

Diagnosis: congenital debility

His growth and motor development were satisfactory he sat up at 7 months and walked at 15–16 months. His motor pattern was normal. *Mental retardation was not* observed. He began to talk at 3 years, with certain consonant defects.

There was family history of delay in talking.

At follow-up, when he was 8½ years old, his speech was still faulty he had trouble with the articulation of k, g and s. The physical and neurological examination was normal. His vision and hearing were felt to be normal. His mental development was considered normal for his age.

An EEG was recommended, but the parents refused.

Diagnoses: retardation of speech, mild dysphasia.

No. 46 (7156/3/1953)

A boy born at term in private clinic on July 21 1953, to a multipara following normal pregnancy The delivery which was uncomplicated, was stimulated by injections, and morphia was given. The infant was not asphyxiated and appeared normal for the first 24 hours except for a certain flaccidity On the second day he was, however admitted to the DPGs because f cyanotic attacks with diagnosis of suspected debility On admission he was somewhat flaccid and trembling with grunting respiration. During the next 4 days he had repeated cyanotic attacks with decreasing frequency His breathing became normal within couple of days, and his trembling subsided. *He was treated with oxygen for four days* and was discharged on the 6th day in apparently good condition.

Diagnosis: congenital debility

His growth as well as motor and mental development were *satisfactory He* was able to walk before the age of one year and his motor pattern was normal. His vision and hearing were also normal. He started saying single words at an early age. However he was unable to form sentences until he was 4½ years old, and his pronunciation was faulty His behaviour had always been rather aggressive.

At follow-up, when he was 5 years old, his physical development was considered to be normal for his age. He was thought to be somewhat backward, but his behaviour appeared normal during the examination. Several consonants were mispronounced. The neurological examination was normal. An EEG was normal. H was referred to speech therapist, who found imperfect pronounciation of consonants and a few agrammatical errors. His diagnoses were speech retardation; expressive and, probably mild receptive aphasia. The child was referred to the Institute for Speech Disorders at the age of 6 years. At this time psychological testing was carried out, revealing an IQ of 101 His ability to concentrate was good. On Bender-Goldstein tests slight visuo-motor defects suggesting organic cerebral damage were demonstrated.

Diagnoses: speech retardation, expressive (and possibly receptive) aphasia.

N 47 (20335/3 1954)

A girl born at home at term on Jan. 21 1954, to a primipara following normal pregnancy The delivery was normal. No record of labour stimulation is vailable, but 0 7 ml pethidine was given. The cord was wound around the infant's neck, but she was not asphyxiated. Because of cyanotic attacks she was admitted to the DPGs during the first 24 hours with diagnosis of asphyxia. On admission she was flaccid and her respiration was grunting. She sustained repeated cyanotic attacks during the first 24 hours only Her respiration and muscle tone quickly became normal. She was discharged 3 days later in pparently good condition.

Diagnosis: congenital debility

second day he was admitted to the DPGe because of suspected intracranial haemorrhage and hyperpyrexia (39 C). On admission he was restless and trembling, but not rigid, his colour was good He recovered quickly and his temperature fell to normal within 24 hours. He was discharged after 6 days in apparently good condition.

The diagnosis: suspected intracranial haemorrhage.

His growth was normal, as was his motor development, though for the first few months he was rather flaccid and listless he did not smile until 5 months or sit up until about 9 months, but walked at 15 months. The motor pattern was normal. His mental development was apparently quite satisfactory Nevertheless the family doctor suspecting retarded development, had him referred, at 2½ years, for psychological examination. His DQ was found to be 94 at Bühler Hetzer infant-testing. The child was considered of normal intelligence, and the low score recorded was thought to be due to his speech defect. His speech, which was bizarre and almost unintelligible, was interpreted as an isolated expressive aphasia. There were no receptive speech disorders. He was restless and could not concentrate, which was ascribed to idleness. He was referred to the Institute for Speech Disorders. However shortly after entering kindergarten his speech improved spontaneously and the examination was not carried out.

On follow-up examination, at 5 years 9 months, he was found to be well-developed, physically and mentally The neurological examination was normal. His speech was characterized by mispronounciation of certain consonants (the mother thought it was normal), vocabulary and speech comprehension appeared normal. EEG was not carried out. At about 6 years of age he was again referred to the Institute for Speech Disorders, where he was found to have a slight speech defect. However his greatest problem was, in their opinion, his restlessness and lack of concentration, even though these features had improved. Since schooling problems, particularly in reading, were anticipated, he was referred to a school psychologist with a view to postponing school attendance for a year It is not known, however whether this examination was carried out or not.

Diagnoses. previous mild motor retardation, dysphasia, behaviour difficulties.

No 44 (19894/3/1953)

A boy born at term in a private clinic on Febr 16, 1953 to a multipara, following a normal pregnancy The delivery was prolonged, stimulated by injections repeatedly 1 ml of pethidine was also given. The course was normal. The infant was not asphyxiated however he was admitted to the DPGe at 8 days because of poor sucking and grunting respiration and suspected atelectasis. On admission his breathing was rather laboured, but quickly improved, and no other symptoms were observed. He was discharged in apparently good condition 3 days later

Diagnosis. congenital debility

His later growth, motor and mental development were normal. He began to say single words at 18 months, but was rather late in forming sentences, and there were a few defects of pronounciation.

At follow-up 5 /a years old, he could not talk correctly but his vocabulary was felt to be within normal limits. Hearing was normal. His motor and mental development were also considered normal. Neurological examination was normal.

EEG was recommended, but his parents were not interested

Diagnoses: speech retardation, mild dysphasia.

No 45 (22105/3/1953)

A boy born in a private clinic at term on March 28 1953 to a 30-year-old primipara, following an uncomplicated pregnancy The delivery which was prolonged, was stimulated by injections, pethidine was given and forceps were applied. There was prolonged asphyxia. Methods of resuscitation were not mentioned. The infant was transferred immediately to the DPGe suspected of intracranial haemorrhage. On ad-

She was 4½ years old at follow-up. Her physical and mental development was considered normal for her age. She still had faulty pronunciation of a few consonants, but her vocabulary was considered adequate for her age. There was pronounced convergent strabismus. The neurological examination was normal.

Diagnosis: previous poor growth, convergent squint (familial), speech retardation, mild; dysphasia, mild.

No. 50 (1391/3/1954)

A girl born at home at term on Oct. 5 1954, to a primipara following normal pregnancy. The delivery was prolonged, but otherwise apparently normal. It was stimulated by injections and pethidine was also given. The infant was asphyxiated for about 20 minutes. There is no record of resuscitation. Her condition appeared normal during the first 24 hours of life, but on the second day she developed cyanotic attacks, during which she was drowsy. She was admitted to the DPGs with a diagnosis of asphyxia. On admission she was flaccid and drowsy and she exhibited during the first day four cyanotic attacks. Subsequently she improved rapidly and her condition was normal at discharge, after 6 days.

Diagnosis: congenital debility sequelae of asphyxia.

Growth and development were satisfactory. She sat up at 4 months and walked at 12 months. Her motor pattern was normal. Hearing and vision were also normal. She started to talk at about 18 months, though not properly. At 2½ years she entered kindergarten, after which her speech improved somewhat. Her mental development was satisfactory: she presented no behaviour problems, though she was extremely restless during her first year of life. There was no explanation for this.

When seen at follow-up at 4 years she had developed physically and mentally in line with her age. She pronounced a few consonants incorrectly but her vocabulary was considered adequate for her age. The neurological examination was normal.

Diagnosis: previous hyperactivity slight retardation of speech, mild dysphasia.

No. 51 (1982/3/1954)

A boy born at home at term on April 25, 1954 to a multipara following a normal pregnancy. He was born as first twin by breech presentation. There is no information concerning the use of labour stimulation or morphia. He was not asphyxiated and apparently presented no abnormal features for the first two days. On the third day however he suffered repeated cyanotic attacks and was referred to the DPGs for observation. On admission he was flaccid and sucked poorly. On that day he exhibited further cyanotic attacks, but these were not repeated. His condition improved gradually and he was discharged 9 days later in apparently good condition.

Diagnosis: congenital debility

His growth and development were normal. He walked at the usual time. His vision and hearing were normal. He talked at about 2 years, with some errors of pronunciation. There were no behavioural problems; but he had nocturnal enuresis (which was familial).

At follow-up, at 5 years of age, he had scarcely reached medium height (minus 6 cm), but was well-proportioned and well-nourished. His mental development appeared compatible with his age. He pronounced a few consonants incorrectly but his vocabulary appeared normal. The neurological examination was normal.

Diagnosis: nocturnal (familial) enuresis, mild dysphasia.

No. 52 (768/3/1948)

A boy born at home, possibly 3 weeks beyond term, on Nov 20, 1948, to a multipara of 35 years, following normal pregnancy. The delivery seems to have been normal, use of labour stimulation and morphia is not reported. He was delivered by vigorous manual expulsion. BW 4200 g. There was apparently no asphyxia or other abnormal features during the first 24 hours. On the second day however he

Her growth and development were normal. She walked at one year. Her mental development was satisfactory and she presented no behavioural problems. Her vision and hearing were normal. She was able to say single words before the age of one. However she could not form sentences until she was 3 years of age and her pronounciation was faulty.

At follow-up, 4 ½ years old, she still spoke incorrectly, however her vocabulary was felt to be normal. Her mental development appeared compatible with her age. Her physical development was normal. The neurological examination was normal. EEG was not recorded.

Diagnoses: speech retardation, mild dysphasia.

No 48 (16757/205/1955)

A boy born in a private clinic at term on Oct. 30, 1955, to a multipara of 40 years, following a normal pregnancy. The delivery was prolonged, but otherwise uncomplicated; stimulating injections were given twice; pethidine was also given twice and tetrapon once. There was "prolonged" asphyxia and the infant was given lobeline and artificial respiration. Immediately afterwards he was transferred to the DPGe with a diagnosis of congenital debility. On admission he was restless, trembling and rigid; the rigidity was more pronounced in the right side. Respiraton was grunting. During the first three days the patient exhibited repeated cyanotic attacks, as well as convulsions, which were more pronounced in the right side. There was a high-pitched cry. Oxygen was administered for 3 days, after which the condition became normal, and he was discharged on the 6th day in apparently good condition; follow-up was recommended, however.

Diagnoses: difficult birth, suspected intracranial haemorrhage.

He was seen in the OP-clinic of the DPGe at 6 months and was found to be normal as far as his mental and motor development was concerned. He could sit up alone, was alert and interested. His muscle tone was normal. Growth and development were satisfactory also thereafter. He walked at 11 months and his motor pattern was normal. His vision and hearing were normal. He began to say single words at one year, but at 3 years he could still not form sentences. His pronounciation was correct.

At follow-up, when three years old, his mental and motor development was considered compatible with his age. The neurological examination was normal. His speech was faulty as mentioned. EEG was not recorded.

Diagnosis: speech retardation (?).

No 49 (8623/3/1954)

A girl born in a private clinic at term on July 26, 1954, to a 31 year-old multipara following a normal pregnancy. The delivery was normal, labour stimulation and morphia were not given. There was asphyxia for a few minutes, and cyanotic attacks occurred during the first 24 hours. The infant was therefore transferred to the DPGe. The cyanotic attacks persisted for three days. Repeated convulsions, more pronounced in the right side, were observed during the same period. There was also a bilaterally equal rigidity. From the fourth day onwards there were no further attacks. However on discharge, on the eighth day, there was some rigidity of the back. Her general condition otherwise was good.

Diagnoses: asphyxia neonatorum, suspected intracranial haemorrhage.

Her growth was slow for the first two years, but thereafter improved. During the same period she frequently ground her teeth. There was a convergent squint, but her vision was thought to be good and no treatment was given. (A sister had a squint). The motor development was good. She sat up at 6 months, and walked at one year. The motor pattern was normal. Her hearing was good. She said single words at 2 years and talked by the time she was 3 with faulty pronounciation of a few consonants. Her mental development was satisfactory. No behaviour problems were reported.

to certain problems due to restlessness and hyperactivity. Her vision, hearing and speech were normal. About 4 years of age she suffered a generalized clonic seizure in connection with a febrile illness. There was no other history of convulsions or family history.

At follow-up, 5 years of age, she was found to be normally developed physically as well as mentally. The neurological examination was normal. She had nocturnal enuresis (non-familial). For geographical reasons an EEG was unobtainable.

Diagnosis: febrile convulsions (late onset), behaviour disorder, nocturnal enuresis.

No. 55 (21621/3/1955)

A girl born at home at term on Jan. 14, 1955, to a multipara following a normal pregnancy. Delivery was normal. Labour was not stimulated or morphia given. The infant was not asphyxiated. However, during the first 24 hours she developed cyanosis and apnoea lasting for a few minutes. When these symptoms recurred on the second day, she was admitted to the DPGs. On that day two further attacks occurred, but otherwise no abnormal features were observed, and she was symptomless for the rest of her 6 days' stay. On discharge her condition seemed good.

Diagnosis: congenital debility.

Her growth and development, physical as well as mental, were satisfactory. She walked at 13 months, and her motor pattern was normal. Hearing and speech were normal. Apart from a divergent squint (familial) her vision was normal. At the age of two years she had a generalized clonic convulsion lasting for a few minutes in association with high fever and on two further occasions there was gross trembling in association with fever. There was no familial history of convulsions.

At follow-up, at the age of 4, her physical and mental development were found to be compatible with her age. The neurological examination was normal. She had a slight divergent squint. EEG was normal.

Diagnosis: febrile convulsions, familial divergent squint.

No. 56 (8165/3/1954)

A girl born at home before term on July 18, 1954, to a multipara following a normal pregnancy. She was the second twin. The delivery was apparently normal. Labour stimulating injections were given. There is no record of the use of morphia. BW was 1800 g. The infant was not asphyxiated. (The first born twin died at home on the second day from unknown cause). She was admitted to the DPGs on the second day with diagnosis of prematurity, appeared normal on admission, but suffered repeated cyanotic attacks on the third day of life. Thereafter she was well and 38 days later was discharged in apparently good condition.

Diagnosis: congenital debility, prematurity.

Her growth was satisfactory and her motor development good, she walked at 15 months. Her motor pattern was normal. She had convergent squint (non-familial). Her hearing was normal. She talked "early". Up to the age of 18 months she had several fits described as breath holding spells. (No family history of convulsion reported). Her mental development was satisfactory and she presented no behavioural problems.

She was seen at follow-up aged 4¹/₂ years, at which time her height was 8 cm below average (non-familial); she was well-proportioned, though slight, but well-nourished. Her motor pattern was normal. Mental development appeared normal for her age. The neurological examination was normal. There was mild convergent squint.

Diagnosis: convergent squint, breath holding spells (in the past), small size.

No. 57 (3252/3/1951)

A boy born on June 15, 1951, to a 34-year-old multipara. The pregnancy had been complicated by severe varicose veins and oedema of the legs, and the delivery was therefore induced at term in private clinic. Repeated labour stimulating injections

suffered convulsions and cyanotic attacks and was admitted to the DPGe suspected of birth injury On admission he was flaccid, and his respiration was grunting. He sucked poorly During that day and the following he sustained additional cyanotic attacks and two generalized seizures. His condition improved gradually his respiration and tone became normal, and on discharge, after 19 days stay his condition was considered good.

Diagnosis: intracranial haemorrhage.

His growth was slow throughout his childhood though his motor development was normal. He sat up at 6 months and walked by 10 months. The motor pattern was normal, as were his vision and hearing. He spoke at 2 years. Nocturnal enuresis was present until 9 years (not familial). He started school at 7 years. His progress, however was poor and after 3 months, school attendance was postponed for another year The school psychologist at that time found his IQ to be 80. The next year he did not do much better At the end of the year he was tested again, revealing an IQ of 84 He was particularly poor at arithmetic. The school psychologist found no evidence of brain damage The boy was transferred to a special class, where he did better He presented no behavioural problems.

When seen at follow-up, 11¹/ years old, he was small—20 cm below average height (no family history of small size) and rather slight, but well-proportioned. He appeared backward, but well-balanced. The neurological examination was normal. EEG was normal.

Diagnoses: small size, mental retardation (backwardness), previous nocturnal enuresis.

No 53 (8347/3/1954)

A boy born at home at term on July 22, 1954 to a 33-year-old multipara following a normal pregnancy The delivery was rapid No drugs were given. The infant was asphyxiated for a few minutes. No treatment was given. Because of cyanotic attacks he was admitted to the DPGe during the first 24 hours with a diagnosis of congenital debility During his first day in hospital he exhibited additional attacks of cyanosis as well as intermittent apnoea. Subsequently there were no abnormal features and he was discharged 5 days later in apparently good condition.

Diagnosis. asphyxia neonatorum.

His growth was normal his mental and motor development were satisfactory He walked at 10 months. His vision and hearing were normal. He talked at 2 years of age and presented no behavioural problems. He occasionally ground his teeth at night.

When seen at follow-up, not quite 4 / years old, he was about 10 cm under average height, though well-proportioned and well-nourished. His motor pattern was normal and mental development appeared in line with his age. He still had enuresis at night. (No family history of small size or enuresis).

Diagnoses: small size, nocturnal enuresis.

No. 54 (24866/3/1954)

A girl born in a private clinic before term on March 20, 1954 to a primipara following a normal pregnancy The delivery was normal; stimulating injections or morphia were not given. There was asphyxia for a few (?) minutes, during which lobeline and coramine were given. BW was 2100 g. She was admitted to the DPGe shortly after birth with a diagnosis of congenital debility due to slight respiratory trouble. Her breathing was grunting on admission, but otherwise she was quite well. During her second and third day she sustained additional cyanotic attacks, and her respiration was still laboured but thereafter improved. During the rest of her 17 days stay she presented no abnormal features and her condition appeared good on discharge.

Diagnosis: congenital debility

Her growth and development were good. She walked at one year Her motor pattern was normal and her mental development was satisfactory Her behaviour gave rise

to certain problems due to restlessness and hyperactivity. Her vision, hearing and speech were normal. About 4 years of age she suffered a *generalized clonic seizure* in connection with a febrile illness. There was no other history of convulsions or family history.

At follow-up, 5 years of age, she was found to be normally developed, physically as well as mentally. The neurological examination was normal. She had nocturnal enuresis (non-familial). For geographical reasons an EEG was unobtainable.

Diagnoses: febrile convulsions (late onset), behaviour disorder, nocturnal enuresis.

No. 55 (21621/3/1955)

A girl born at home at term on Jan. 14, 1955 to multipara *following* a normal pregnancy. Delivery was normal. Labour was not stimulated or morphia given. The infant was not asphyxiated. However during the first 24 hours she developed cyanosis and apnoea lasting for few minutes. When these symptoms recurred on the second day she was admitted to the DPGe. On that day two further attacks occurred, but otherwise no abnormal features were observed, and she was symptomless for the rest of her 6 days' stay. On discharge her condition seemed good.

Diagnoses: congenital debility.

Her growth and development, physical as well as mental, were satisfactory. She walked *at 13 months, and her motor pattern* was normal. Hearing and speech were normal. Apart from a divergent squint (familial) her vision was normal. At the age of tw years she had a generalized clonic convulsion lasting *for a few minutes* in association with high fever, and on two further occasions there was gross trembling in association with fever. There was no familial history of convulsions.

At follow-up, at the age of 4, her physical and mental development were found to be compatible with her age. The neurological examination was normal. She had slight divergent squint. EEG was normal.

Diagnoses: febrile convulsions, familial divergent squint.

No. 56 (8165/3/1954)

A girl born at home before term on July 18, 1954, to multipara following a normal pregnancy. She was the second twin. The delivery was apparently normal. Labour stimulating injections were given. There is no record of the use of morphia. BW was 1800 g. The infant was not asphyxiated. (The first born twin died at home on the second day from unknown cause). She was admitted to the DPGe on the second day with a diagnosis of prematurity, appeared normal on admission, but suffered repeated cyanotic attacks on the *third day of life*. Thereafter she was well and 38 day later was discharged in apparently good condition.

Diagnoses: congenital debility, prematurity.

Her growth was satisfactory and he motor development good, she walked at 15 months. Her motor pattern was normal. She had convergent squint (non-familial). Her hearing was normal. She talked early" Up to the age of 18 months she had several fits described as breath holding spells. (No family history of convulsion reported). Her mental development was satisfactory and she presented no behavioural problems.

She was seen at follow-up aged 4½ years, at which time her height was 8 cm below average (non-familial), she was well-proportioned, though slight, but well-nourished. Her motor pattern was normal. Mental development appeared normal for her age. The neurological examination was normal. There was mild convergent squint.

Diagnoses: convergent squint, breath holding spells (in the past), small size.

No. 57 (5252/3.1951)

A boy born on June 15 1951 to 34-year-old multipara. The pregnancy had been complicated by severe varicose veins and oedema of the legs, and the delivery was therefore induced at term in a private clinic. Repeated labour stimulating injections

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGe on the 8th day On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis. congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory Thereafter his condition improved but his height remained subnormal. (Both parents were small). He sat up at 8–9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months–two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever but was thereafter seizurefree.

There was no family history of convulsions.

His mental development and behaviour were satisfactory He started school at the usual time and did well.

When seen at follow-up, at 7 / years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnoses. previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No. 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikethamide was given. She was rather flaccid and sucked poorly She was therefore admitted to the DPGe at 7 days, with a diagnosis of prematurity Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility

Her growth was satisfactory During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later Her motor pattern was normal. Her vision, hearing and speech were also normal and her mental development was satisfactory She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet) however no record could be traced

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnoses: previous motor retardation, previous benign hypotonicity

No 59 (570/1/1946)

A boy born at the RH before term on Oct. 18, 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was aphyxiated for

15 minutes, during which lobeline was given. He sucked poorly but was otherwise normal. Because of the low BW he was transferred to the DPGe on the 12th day. Here his growth was poor for the next 3 weeks, but otherwise he was symptom-free. He was discharged after 42 days in apparently good condition.

Diagnosis: congenital debility

His growth remained unsatisfactory for the first two years, but he exhibited no specific symptoms. His motor development during that time was slow; no information was available concerning the age at which he could sit up; however he did not start walking until he was well over 2 years old. His motor pattern was normal, as were his vision and hearing. He talked at 2 years. His mental development and behaviour were satisfactory. He started school at the usual time, but his progress was only fair despite an IQ-score of 132 in the first year. Reading presented his main problem and he was given special lessons from the second to the fifth year. It was not until he was 13–14 years that he overcame his reading defect partially. There was no family history of dyslexia.

When seen at follow-up, well over 11 / years old, his physical development was found to be normal for his age, and mentally he appeared normal.

Diagnoses: previous motor retardation, previous poor growth, dyslexia.

No. 60 (678/3/1946)

A boy born on March 20, 1946, to multipara following normal pregnancy. The delivery was induced at home, when the mother had failed to feel foetal movements for 36 hours. It was prolonged, but otherwise normal. Several stimulant injections were given. The use of morphia is not reported. The infant had the cord wound around his neck, but apparently was not asphyxiated. He was admitted to the DPGe in the first 24 hours because of cyanosis and fever with diagnosis of heart disease and bronchopneumonia. On admission his colour was poor but his respiration appeared normal. X-rays of the chest at first supported the diagnosis of heart disease, but repeat X-ray gave no confirmation and auscultation also was normal. He sucked poorly and had to be given oxygen for the first 5 days. During this period he also exhibited cyanotic attacks, in spite of being given oxygen. From the 5th to the 10th day he was markedly flaccid, though his colour improved. There was no change in tone for the first four days. He recovered slowly and was discharged 5 weeks later in apparently good condition.

Diagnosis: congenital debility

His growth was good, during his first two years his weight was even above average. He was also markedly flaccid. At 9 months he was re-admitted to the DPGe because of pneumonia. He was found to be obese and flaccid. The neurological examination was normal. He did not sit up until he was 10 months old and walked at the age of two years. Prior to that he had for some months received walking and foot exercises for what was described as clubfoot. His motor pattern otherwise was normal, though he had always been rather slow without being particularly clumsy. He had experienced no difficulty with fine movements of the fingers. His vision and hearing were normal. He talked at the "usual" time. His mental development had been satisfactory and there were no behaviour problems. He started school at the usual time and did well, although he was dyslectic and received special education for some time.

He was followed-up at more than 12 years of age. His physical condition was normal for his age. The neurological examination was normal. His motor pattern including fine co-ordination of movements was normal, though he ran rather slowly probably because of rather pronounced flatfeet. There was no evidence of heart disease. Intellectually he was considered normal, but rather slow.

EEG had not been carried out.

Diagnoses: previous motor retardation, previous benign hypotonicity, bilateral pes planus, dyslexia.

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGe on the 8th day. On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis: congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory. Thereafter his condition improved but his height remained subnormal. (Both parents were small). He sat up at 8–9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months–two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever but was thereafter seizurefree.

There was no family history of convulsions.

His mental development and behaviour were satisfactory. He started school at the usual time and did well.

When seen at follow-up, at 7 / years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnoses. previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No. 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy. The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikethamide was given. She was rather flaccid and sucked poorly. She was therefore admitted to the DPGe at 7 days, with a diagnosis of prematurity. Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility

Her growth was satisfactory. During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later. Her motor pattern was normal. Her vision, hearing and speech were also normal, and her mental development was satisfactory. She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet); however no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnoses: previous motor retardation, previous benign hypotonicity

No. 59 (570/1/1946)

A boy born at the RH before term on Oct. 18 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was aphyxiated for

15 minutes, during which lobeline was given. He sucked poorly but was otherwise normal. Because of the low BW he was transferred to the DPGe on the 12th day. Here his growth was poor for the next 3 weeks, but otherwise he was symptom-free. He was discharged after 42 days in apparently good condition.

Diagnosis: congenital debility

His growth remained unsatisfactory for the first two years, but he exhibited no specific symptoms. His motor development during that time was slow: no information was available concerning the age at which he could sit up; however he did not start walking until he was well over 2 years old. His motor pattern was normal, as were his vision and hearing. He talked at 2 years. His mental development and behaviour were satisfactory. He started school at the usual time, but his progress was only fair despite an IQ-score of 132 in the first year. Reading presented his main problem and he was given special lessons from the second to the fifth year. It was not until he was 13–14 years that he overcame his reading defect partially. There was no family history of dyslexia.

When seen at follow-up, well over 11 / years old, his physical development was found to be normal for his age, and mentally he appeared normal.

Diagnoses: previous motor retardation, previous poor growth, dyslexia.

No. 60 (678/3/1946)

A boy born on March 20, 1946, to a multipara following a normal pregnancy. The delivery was induced at home, when the mother had failed to feel foetal movements for 36 hours. It was prolonged, but otherwise normal. Several stimulant injections were given. The use of morphia is not reported. The infant had the cord wound around his neck, but apparently was not asphyxiated. He was admitted to the DPGe in the first 24 hours because of cyanosis and fever with a diagnosis of heart disease and bronchopneumonia. On admission his colour was poor but his respiration appeared normal. X-rays of the chest at first supported the diagnosis of heart disease, but repeat X-rays gave no confirmation and auscultation also was normal. He sucked poorly and had to be given oxygen for the first 5 days. During this period he also exhibited cyanotic attacks, in spite of being given oxygen. From the 5th to the 10th day he was markedly flaccid, though his colour improved. There was no change in tone for the first four days. He recovered slowly and was discharged 5 weeks later in apparently good condition.

Diagnosis: congenital debility

His growth was good; during his first two years his weight was even above average. He was also markedly flaccid. At 9 months he was re-admitted to the DPGe because of pneumonia. He was found to be obese and flaccid. The neurological examination was normal. He did not sit up until he was 10 months old and walked at the age of two years. Prior to that he had for some months received walking and foot exercises for what was described as clubfoot. His motor pattern otherwise was normal, though he had always been rather slow without being particularly clumsy. He had experienced no difficulty with fine movements of the fingers. His vision and hearing were normal. He talked at the "usual" time. His mental development had been satisfactory and there were no behaviour problems. He started school at the usual time and did well, although he was dyslectic and received special education for some time.

He was followed-up at more than 12 years of age. His physical condition was normal for his age. The neurological examination was normal. His motor pattern including fine co-ordination of movements was normal, though he ran rather slowly probably because of rather pronounced flatfeet. There was no evidence of heart disease. Intellectually he was considered normal, but rather slow.

EEG had not been carried out.

Diagnoses: previous motor retardation, previous benign hypotonicity, bilateral pes planus, dyslexia.

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated, but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGe on the 8th day On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days stay he was discharged in apparently good condition.

Diagnosis. congenital debility

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory Thereafter his condition improved, but his height remained subnormal. (Both parents were small). He sat up at 8–9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months–two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever but was thereafter seizurefree.

There was no family history of convulsions.

His mental development and behaviour were satisfactory He started school at the usual time and did well.

When seen at follow up, at 7 /₂ years of age, his height was 10 cm below average, but he was well-proportioned and well-nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnoses: previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikethamide was given. She was rather flaccid and sucked poorly She was therefore admitted to the DPGe at 7 days, with a diagnosis of prematurity Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis. congenital debility

Her growth was satisfactory During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later Her motor pattern was normal. Her vision, hearing and speech were also normal, and her mental development was satisfactory She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet), however no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnoses. previous motor retardation, previous benign hypotonicity

No 59 (570/1/1946)

A boy born at the RH before term on Oct. 18, 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was aphyxiated for

15 minutes, during which lobaline was given. He sucked poorly but was otherwise normal. Because of the low BW he was transferred to the DPGe on the 12th day. Here his growth was poor for the next 3 weeks, but otherwise he was symptom-free. He was discharged after 42 days in apparently good condition.

Diagnosis: congenital debility

His growth remained unsatisfactory for the first two years, but he exhibited no specific symptoms. His motor development during that time was slow; no information is available concerning the age at which he could sit up; however he did not start walking until he was well over 2 years old. His motor pattern was normal, as were his vision and hearing. He talked at 2 years. His mental development and behaviour were satisfactory. He started school at the usual time but his progress was only fair despite an IQ-score of 132 in the first year. Reading presented his main problem and he was given special lessons from the second to the fifth year. It was not until he was 13–14 years that he overcame his reading defect partially. There was no family history of dyslexia.

When seen at follow-up, well over 11 ½ years old, his physical development was found to be normal for his age, and mentally he appeared normal.

Diagnoses: previous motor retardation, previous poor growth, dyslexia.

No. 60 (678/3/1946)

A boy born on March 20, 1946, to a multipara following a normal pregnancy. The delivery was induced at home, when the mother had failed to feel foetal movements for 36 hours. It was prolonged, but otherwise normal. Several stimulant injections were given. The use of morphia is not reported. The infant had the cord wound around his neck, but apparently was not asphyxiated. He was admitted to the DPGe in the first 24 hours because of cyanosis and fever with a diagnosis of heart disease and bronchopneumonia. On admission his colour was poor but his respiration appeared normal. X-rays of the chest at first supported the diagnosis of heart disease, but repeat X-rays gave no confirmation and auscultation also was normal. He sucked poorly and had to be given oxygen for the first 5 days. During this period he also exhibited cyanotic attacks, in spite of being given oxygen. From the 5th to the 10th day he was markedly flaccid, though his colour improved. There was no change in tone for the first four days. He recovered slowly and was discharged 5 weeks later in apparently good condition.

Diagnosis: congenital debility

His growth was good during his first two years his weight was even above average. He was also markedly flaccid. At 9 months he was re-admitted to the DPGe because of pneumonia. He was found to be obese and flaccid. The neurological examination was normal. He did not sit up until he was 10 months old and walked at the age of two years. Prior to that he had for some months received walking and foot exercises for what was described as clubfoot. His motor pattern otherwise was normal, though he had always been rather slow without being particularly clumsy. He had experienced no difficulty with fine movements of the fingers. His vision and hearing were normal. He talked at the "usual" time. His mental development had been satisfactory and there were no behaviour problems. He started school at the usual time and did well, although he was dyslectic and received special education for some time.

He was followed-up at more than 12 years of age. His physical condition was normal for his age. The neurological examination was normal. His motor pattern including fine co-ordination of movements was normal, though he ran rather slowly probably because of rather pronounced flatfeet. There was no evidence of heart disease. Intellectually he was considered normal, but rather slow.

EEG had not been carried out.

Diagnoses: previous motor retardation, previous benign hypotonicity, bilateral pes planus, dyslexia.

were given and the delivery was quick. There is no record of morphia being given. The course was otherwise normal. The infant was not asphyxiated, but rather flaccid, and four hours after birth sustained a cyanotic attack. During the next few days he remained flaccid and had additional cyanotic attacks. He was therefore admitted to the DPGe on the 8th day. On admission he was rather flaccid and his respiration was laboured. During the first few days there were a number of cyanotic attacks, but subsequently his condition improved and after 6 days' stay he was discharged in apparently good condition.

Diagnosis: congenital debility.

During the first 8 months he was somewhat flaccid and listless, and his growth was unsatisfactory. Thereafter his condition improved, but his height remained subnormal. (Both parents were small). He sat up at 8–9 months and walked at 14 months. His motor pattern, vision and hearing were normal. He talked at 18 months–two years. At about one year he sustained an attack of generalized clonic convulsions in association with high fever, but was thereafter seizurefree.

There was no family history of convulsions.

His mental development and behaviour were satisfactory. He started school at the usual time and did well.

When seen at follow up, at 7¹/₄ years of age, his height was 10 cm below average, but he was well-proportioned and well nourished. His motor pattern was normal as was the neurological examination. Auscultation revealed a rough systolic murmur maximal in the third left intercostal space. There was no evidence of cardiac failure and he had no cardiac complaints. His mental development was felt to be in line with his age.

Diagnoses: previous motor retardation, congenital heart disease (VSD?), febrile convulsion, small height.

No 58 (30/3/1946)

A girl born at a private clinic before term on April 6, 1946, to a 17 year-old primipara following a normal pregnancy. The delivery was uncomplicated. Analgesics were given, but labour stimulating drugs were not. BW was 2000 g. The infant was asphyxiated for a few minutes, during which nikethamide was given. She was rather flaccid and sucked poorly. She was therefore admitted to the DPGe at 7 days, with a diagnosis of prematurity. Her growth was poor for the first month, then improved, as did her muscle tone. She presented no other abnormal features and was discharged after 67 days in apparently good condition.

Diagnosis: congenital debility.

Her growth was satisfactory. During the first 18 months or so she was flaccid, but not apathetic. She did not sit up until she was 18 months and walked a few months later. Her motor pattern was normal. Her vision, hearing and speech were also normal, and her mental development was satisfactory. She started school at 7 years and did well. Her behaviour was normal. When 4 years old she purportedly had an afebrile episode of unconsciousness lasting for several hours and possibly associated with convulsion. She was said to have been admitted to hospital (Blegdamshospitalet); however, no record could be traced.

When seen at follow-up, aged 13 years, her physical and mental development was felt to be normal for her age. The neurological examination was normal. EEG was not available.

Diagnoses: previous motor retardation, previous benign hypotonicity.

No 59 (570/1/1946)

A boy born at the RH before term on Oct. 18, 1946, to a multipara. The pregnancy was complicated by hypertension and vaginal bleeding during the third month. Blood transfusion was given. The delivery was rapid. Morphia was given. There was profuse bleeding owing to placenta praevia. BW was 1900 g. The infant was aphyxiated for

to talk at 18 months, and his pronunciation was correct. His mental development was satisfactory and there were no behaviour problems.

At the age of 3, at follow-up, he was found to be physically and mentally developed according to his age. The neurological examination was normal.

Diagnosis: previous motor retardation, previous benign hypotonicity

No. 64 (18791/3/1955)

A girl born at term at home on Oct. 31 1955 to a multipara, who suffered rubella during the third month of gestation. The delivery was uncomplicated, labour stimulation and morphia were not applied. *BW was 2900 g. The infant was not asphyxiated, but listless, flaccid* and sucked poorly However she was not admitted to the DPGe until 3 eeks later. The diagnosis was prematurity suspected intracranial haemorrhage. On admission the above mentioned features were observed. Subsequently there were arying opinions on her muscle tone; one examiner *found it to be upper borderline* normal. At discharge it was normal. 2 3 weeks after admission her growth became satisfactory and she was discharged after 29 days in apparently good condition.

Diagnosis: congenital debility suspected intracranial haemorrhage.

Since her growth and development were slow she was *readmitted at the age of* 4 months. The examination revealed marked rickets, and because of increased tendon reflexes and certain tension of the adductor muscles in the legs spasticity was suspected. The child was in poor condition and emaciated. A gluten-free diet was tried ith no results.

Her growth remained unsatisfactory until the age of 2 years; after which it improved. During this period she was also listless, flaccid and her need for sleep was great. Her motor development was slow she did not sit up until she was 9–10 months and alked at about *20 months. Her motor pattern* appeared normal. Her vision, hearing and speech were normal.

She was seen at follow-up before she was 3½ years old. Her height and weight are average. Head circumference was lower borderline normal (48 cm). Her intellectual development seemed in line with her age. The neurological examination was normal.

Diagnosis: previous motor retardation, previous hypotonicity previous poor growth, previous rickets.

No. 65 (934/3/1948)

A boy born at home before term on Jan. 9 1948, to multipara following normal pregnancy During the delivery quinine was administered. In addition labour stimulant injections were given three times, but no morphia was given. Otherwise the course seemed to have been normal. BW was 1800 g. The infant was not asphyxiated. He sucked poorly and did not gain weight at home but was otherwise apparently normal. He was admitted to the DPGe at 19 day with diagnosis of congenital debility Apart from persistently poor sucking and slow growth he exhibited no abnormal features during the 64 days in hospital. He was discharged in apparently good condition.

Diagnosis: prematurity congenital debility

His growth was unsatisfactory for further 2 months. However from the age of four months it improved. His *motor development* was slow he did not sit up until he was one year old and did not walk until over 18 months old. His *motor pattern* was felt to be normal. His vision, hearing and speech ere also normal; he talked at 2 3 years. His mental development was fairly good. He started school at the usual time, but had to repeat the first form. Thereafter his progress was satisfactory but he had reading difficulties and was thought to be mildly dyslectic. There were no major behaviour problems; he got on quite well with other children, but had somewhat violent temperament. He had been psychologically tested twice, but the outcome is not known.

When he was seen at follow-up, at the age of 10, his physical development was

No 61 (14446/3/1952)

A girl born in a private clinic before term on Dec. 1 1952, to a multipara following normal pregnancy The delivery was normal. Pethidine was given, there was no record of labour stimulation. BW 2000 g. The infant was not asphyxiated, but was immediately admitted to the DPGo because of low BW On admission the respiration was grunting and during the first 4 hours there were a few cyanotic attacks. Oxygen was given for 4 days, and thereafter the respiration became normal. The infant revealed no further abnormalities and was discharged after 22 days in apparently good condition.

Diagnoses: prematurity suspected intracranial haemorrhage.

The subsequent growth was satisfactory The motor development was fairly satisfactory She sat up at 6 months, but did not walk until 2 years of age. The motor pattern was normal. Vision, hearing, speech, mental development and behaviour were normal. She had, however been very restless for no apparent reason during the first two years of life. She was expected to be ready for school at the usual time.

On follow-up, at the age of 6, her physical and mental development was found to be normal. The neurological examination was normal.

Diagnoses: previous motor retardation, previous hyperactivity

No. 62 (7215/3/1954)

A boy born in a private clinic at term on July 6 1954 to a primipara following a normal pregnancy The membranes had ruptured 2 days prior to delivery but labour did not occur Hence the delivery was stimulated by several injections. There was no record of morphia being used. The course was uncomplicated. BW was 2750 g. He was not asphyxiated but suffered a cyanotic attack on the first day and was referred to the DPGe. On admission he was trembling and his respiration grunting. However he recovered within a day or so and the cyanotic attacks did not recur He was discharged on the 8th day in apparently good condition.

Diagnosis: sequelae of difficult delivery

His growth was poor for the first few months, during which he was also very listless. Subsequently he gradually became more active, and his growth improved He sat up at 8–9 months and walked at 14 months. His motor pattern was normal. At the age of 6 months impaired hearing was suspected but this was not confirmed. He talked when well over 2 years old. His vision was normal. His mental development and behaviour were satisfactory

On follow-up examination, at the age of 4 ¼ years, his physical and mental development was found to correspond to his age. The neurological examination was normal.

Diagnoses: previous mild motor retardation, previous poor growth.

No. 63 (16182/55)

A boy born at home at term on Oct. 23 1955 to a multipara, following a normal pregnancy The delivery was uncomplicated. Labour stimulation but no morphia was given. There is no mention of asphyxia, however lobeline was given. The infant was referred to the DPGo immediately after birth diagnosed as Rhesus baby" the mother being Rh-negative. The infant, however was also Rh negative, and did not develop jaundice. On admission he was flaccid with grunting respiration and during the first 24 hours exhibited two cyanotic attacks. He recovered rapidly and oxygen therapy was discontinued after 2 days. The flaccidity disappeared within forty-eight hours, and thereafter he appeared normal until his discharge on the 5th day

Diagnosis, congenital debility

During the first 10 months of his life the parents suspected brain damage, since he appeared very listless and passive. He did not smile and focus until he was 6 months old he did not sit up until 10 months. From then on he started to develop rapidly and in a normal way He walked at 14 months, and his motor pattern was normal. His vision and hearing were felt to be within normal limits. He began

stimulation or morphia being used. The infant was not asphyxiated. However she was admitted to the DPGe within the first 24 hours because of cyanotic attacks and an episode of generalized convulsions, with a diagnosis of intracranial haemorrhage, cephalhaematoma. The latter was confirmed, but no other abnormalities were found during her 7 days stay and she was discharged in apparently good condition.

Diagnosis: suspected congenital debility

Her growth and development were normal. She walked when over one year of age, and her motor pattern, mental development, vision, hearing and speech were all normal. She talked at 18 months. During the first two years of life she was markedly restless, for which no external cause could be found. Her need for sleep was very reduced. After that time her behaviour was unremarkable; she played well and was quiet.

When seen at follow-up at 5 years of age she was well above average height and well-nourished. Her physical development was compatible with her age. Her intelligence was felt to be normal. The neurological examination was normal.

Diagnosis: previous hyperactivity

No. 69 (14942/3/1954)

A boy born in a private clinic at term on Oct. 15 1954, to a primipara of 24 years, following a normal pregnancy. The delivery was induced, but the indication for this is not clear. Repeated stimulant injections were given, as well as morphia. The course was prolonged. As no progress was made, despite adequate labour forceps were applied. The infant was apparently not asphyxiated, nor did he present any abnormal features during the early days of life. However he was admitted to the DPGe on the fifth day because of suspected intracranial haemorrhage. On admission he was cold and flaccid, however his colour was good. He sucked poorly but recovered quickly without presenting additional symptoms. After 6 days he was discharged in apparently good condition.

Diagnosis: sequelae of difficult birth, suspected intracranial haemorrhage.

His growth, physical and mental development, vision, hearing and speech were all normal. The only abnormal feature observed was marked restlessness during the first 9 months or so. No external cause for this could be established.

He was seen at follow-up at the age of 4 years. His physical and mental development was compatible with his age and the neurological examination was normal.

Diagnosis: previous hyperactivity

No. 70 (1867/3/1955)

A boy born in a private clinic at term on April 25 1955 to a primipara following a normal pregnancy. The delivery was uncomplicated, though powerful stimulation by drugs was applied and morphia was given. The infant exhibited prolonged asphyxia, during which lobeline, oxygen and artificial respiration were given. Immediately after birth, when transferred to the DPGe, he was flaccid, cyanosed and apnoeic. He was given oxygen, and following two hours of artificial respiration and 0.2 ml of lobeline his respiration became spontaneous and gradually regular. He was given oxygen for two days, after which his colour remained satisfactory when oxygen was discontinued. He presented no further symptoms thereafter and was discharged after 6 days, in apparently good condition.

Diagnosis: asphyxia neonatorum.

He was seen in OP of the DPGe at 3 months. His growth had been satisfactory and his development good. No neurological signs were demonstrated.

His growth remained satisfactory and his motor development was also adequate. He sat up at 6 months and walked at 12. His motor pattern, vision, hearing and speech were normal. He talked at 2 years. His mental development and behaviour were good, though he was extremely restless during the first 18 months, and particularly during sleep. This feature could not be explained by environmental factors.

Diagnosis: previous hyperactivity

compatible with his age. Mentally he appeared essentially normal, though perhaps somewhat backward The neurological examination was normal. EEG was recommended, but refused by his parents.

Diagnoses, previous motor retardation, minor behaviour difficulties, previous poor growth, mild mental retardation? dyslexia?

No 66 (6375/3/1952)

A boy born in a private clinic almost at term on July 15, 195.., to a primipara, who during pregnancy repeatedly had experienced slight vaginal bleeding. The delivery was prolonged and several stimulant injections were given, besides pethidin on two occasions. The course was otherwise uncomplicated. BW was 2400 g. The infant was asphyxiated for a few minutes during which he was given coramine and lobeline. On the fifth day he was transferred to the DPGe because of suspected intracranial haemorrhage. He had been restless and had sucked poorly and continued to present these features during admission. His respiration was somewhat grunting to begin with, but was quickly restored to normal. He recovered within a few days and his growth gradually became satisfactory He was discharged after 21 days in apparently good condition

Diagnosis, congenital debility

His growth was unsatisfactory for two years and then improved. He was followed-up as OP at the RH at 9 months of age because of anorexia. X-rays revealed no organic explanation for this feature. His motor development at first was slow he sat up at 11 months, walked at 15 months. His motor pattern, vision, hearing and speech were all normal. He talked properly at 18 months. His mental development was satisfactory He was rather restless, which might, to a large extent, be explained by sibling-jealousy

When seen at follow-up, not yet 6½ years old, his height was just below average (minus 5 cm), but he was well-proportioned and well-nourished. His motor pattern was normal. His mental development was felt to be adequate. The neurological examination was normal so was EEG

Diagnoses: previous moderate motor retardation, previous poor growth.

No 67 (8703/3/1951)

A boy born at term in a private clinic on Aug. 29 1951 to a 35-year-old multipara, following an uncomplicated pregnancy The delivery was induced by rupture of the membranes and injections, though the indication for this is obscure. Morphia was not given. The course was uncomplicated. The infant was not asphyxiated. He was transferred to the DPGe within the first 24 hours because of flaccidity and cyanotic attacks, the diagnosis being suspected tentorial tear On admission there was flaccidity and grunting respiration, and during the first 3 days there were several cyanotic attacks. Following oxygen therapy he improved, his tone and respiration became normal and he was discharged after 8 days in apparently good condition.

Diagnosis, congenital debility

His growth and development were satisfactory He sat up at 6 months, walked at 14 months, and his motor pattern, mental development and behaviour were normal He was expected to be ready for school at the usual time. His vision, hearing and speech were normal. During his first two years of life he was very restless and screaming, and his sleep was disturbed. These features gradually subsided. Precipitating factors in his environment were not disclosed.

When followed-up at 6 years 8 months of age his physical and mental development was found to be compatible with his age The neurological examination was normal.

Diagnosis: previous hyperactivity

No 68 (61/3/1953)

A girl born at home at term on April 1 1953 to a 35-year-old multipara, following an uncomplicated pregnancy The delivery was normal. There is no record of labour

but no morphia. The course was uncomplicated. The infant was asphyxiated for about 15 minutes and was given lobeline. Two hours after birth he was admitted to the DPGs with diagnosis of congenital debility. On admission he exhibited flaccidity and grunting respiration; his colour was good except for harlequin colour change on two occasions. He made a rapid recovery and was discharged after 4 days in apparently good condition.

Diagnosis: congenital debility.

His growth and motor development were normal. He walked by the time he was one and his motor pattern was normal. His vision and hearing were good. He had mild squint (familial). He talked at about 2–3 years; his mental development was felt to be normal, though he had a "nervous disposition" and was easily frightened. He also exhibited violent temper tantrums and there was nocturnal teeth grinding with decreasing frequency.

He was mentally and physically developed in line with his age, when seen at follow up at 4½. His behaviour appeared normal during the examination. Neurological examination and EEG were normal.

Diagnosis: behaviour disorder, convergent squint (familial).

No. 74 (9402/3/1954)

A boy born in a private clinic at term on Aug. 11 1954 to a multipara of 40 years (her last delivery had occurred 17 years earlier). The pregnancy was uneventful. Because the delivery did not progress, repeated stimulant injections were given. There is no record of the use of morphia. The course was otherwise normal. The cord was wound around the infant's neck. He was asphyxiated for a few minutes and was given lobeline. Within the first 4 hours he was admitted to the DPGs because of generalized convulsions. On admission his colour was good, but he was markedly rigid and during the second day of life again developed generalized clonic seizure. His tone quickly returned to normal and his condition thereafter was normal. He was discharged after 5 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

Re-examination at 3 months was recommended. However he failed to attend at that time.

His growth and motor development were satisfactory: he walked at one year. His vision, hearing and speech were normal. He talked adequately at 2–3 years. His mental development was satisfactory though he was markedly restless. His mother admitted to his being quite spoiled.

When seen on follow-up examination at four years his physical development was compatible with his age, though he seemed rather babyish; his intelligence was felt to be adequate. An EEG carried out one year later was normal. At that time he was still very fidgety and irritable. A psychological examination was suggested, but could not be carried out.

Diagnosis: behaviour difficulties.

No. 75 (403/3/1947)

A boy born in a private clinic at term on Aug. 31 1947 to a primipara following a normal pregnancy. The delivery was prolonged, but apparently uncomplicated. No information is available concerning labour stimulation or morphia. BW was 4200 g. The cord was wound around the infant's neck, and he was asphyxiated for about 20 minutes, during which time he was given oxygen, artificial respiration, lobeline and cardiazol. He developed generalized clonic convulsion and was immediately transferred to the DPGs with a diagnosis of tentorial tear. On admission he was rigid, and during the first 3 days of life he had several convulsions. His muscle tone gradually returned to normal and no other abnormal features were observed. He was discharged after 18 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth and motor development were good, he sat up at 6 months and walked

No 71 (20844/3/1955)

A girl born at the RH at term on Dec. 7 1955 to a multipara following a normal pregnancy The delivery was prolonged, but uncomplicated. One labour stimulating injection but no morphia was given. The infant was not asphyxiated. However because of cyanotic attacks during the first 24 hours she was transferred to the DPGe suspected of a heart defect. Chest X rays revealed atelectasis, but no evidence of heart disease, and auscultation was also normal. On admission she was flaccid, and presented grunting respiration as well as cyanotic attacks, which persisted until the 4th day or so. After that date her colour and respiration were normal she was still rather flaccid and sucked poorly Her muscle tone was gradually restored to normal, but her growth remained poor At 3 weeks she developed a severe gastro-enteritis caused by Coli 111 She was treated with parenteral fluids and antibiotics and improved fairly rapidly From about one month of age her growth improved. She was discharged after 50 days apparently in good condition but follow-up was recommended.

Diagnoses: asphyxia, gastro-enteritis (Coli 111).

Her growth was satisfactory and her motor development good. She sat up at 6 months, but did not walk until 18 months. Her motor pattern, vision, hearing and speech were all normal. She talked at about 2 /₂ years. Her mental development was satisfactory However during her first two years of life she showed conspicuous restlessness and fits of screaming for no obvious reasons. Thereafter she was still rather lively but cheerful, and there was no further unmotivated restlessness.

When followed-up at over 3 years of age her height was just below average however she was well-proportioned and well-nourished, and her motor pattern was normal Mental development appeared compatible with her age. The neurological examination was normal.

Diagnosis. previous hyperactivity

No 72 (15934/3/1952)

A boy born in a private clinic at term on Dec. 29 1952, to a 34-year-old multipara following a normal pregnancy The delivery was normal stimulant injections were given twice and full anaesthesia was applied. BW was 4000 g. There is no record of asphyxia, but lobeline was given. He was admitted to the DPGe on the first day because of cyanotic attacks and suspected pulmonary atelectasis. During that day he sustained two further cyanotic attacks, but these were not repeated, and he was otherwise normal and able to be discharged 2 days later in apparently good condition.

Diagnosis. aspiration into the lungs.

His growth and motor development were normal. He sat up early" and walked at 15 months. His motor pattern was normal. He had a squint. Diminished visual acuity in the right eye was disclosed and glasses were provided. His parental grandfather also had a squint. His hearing was normal. He spoke by the time he was 2–3 years with a transitory stammer His mental development was satisfactory though he was irritable and sensitive. He was also over-sensitive to noise.

On follow-up, at the age of 5 /₂, his physical development was compatible with his age. Mentally he appeared normal though somewhat reserved. His speech was normal. He had a squint and still wore glasses. He had just been seen by an opthalmologist, who on a previous consultation had found only 5 per cent vision in the right eye, but now reported some improvement. The neurological examination was normal, EEG was normal. Psychological examination could not be carried out. —It was later reported that he had begun school at just under 7 years of age and made good progress.

Diagnoses. behaviour disorder convergent squint (familial).

No 73 (2265/3/1954)

A boy born in a private clinic at term on May 1 1954 to a primipara following a normal pregnancy The delivery was prolonged. Stimulant injections were given.

but no morphia. The course was uncomplicated. The infant was asphyxiated for about 15 minutes and was given lobeline. Two hours after birth he was admitted to the DPGo with a diagnosis of congenital debility. On admission he exhibited flaccidity and grunting respiration, his colour was good except for harlequin colour change on two occasions. He made a rapid recovery and was discharged after 4 days in apparently good condition.

Diagnosis: congenital debility.

His growth and motor development were normal. He walked by the time he was one and his motor pattern was normal. His vision and hearing were good. He had a mild squint (familial). He talked at about 2–3 years; his mental development was felt to be normal, though he had a nervous disposition and was easily frightened. He also exhibited violent temper tantrums and there was nocturnal teeth grinding with decreasing frequency.

He was mentally and physically developed in line with his age, when seen at follow up at 4½. His behaviour appeared normal during the examination. Neurological examination and EEG were normal.

Diagnoses: behaviour disorder, convergent squint (familial).

No. 74 (9802/3/1954)

A boy born at a private clinic at term on Aug. 11 1954, to a *multipara of 40 years* (her last delivery had occurred 17 years earlier). The pregnancy was uneventful. Because the delivery did not progress, repeated stimulant injections were given. There is no record of the use of morphia. The course was otherwise normal. The cord was wound around the infant's neck. He was asphyxiated for a few minutes and was given lobeline. Within the first 24 hours he was admitted to the DPGo because of generalized convulsions. On admission his colour was good, but he was markedly rigid and during the second day of life again developed generalized clonic seizure. His tone quickly returned to normal and his condition thereafter was normal. He was discharged after 5 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

Re-examination at 3 months was recommended. However he failed to attend at that time.

His growth and motor development were satisfactory: he walked at one year. His vision, hearing and speech were normal. He talked adequately at 2–3 years. His mental development was satisfactory though he was markedly restless. His mother admitted to his being quite spoiled.

When seen on follow-up examination at four years his physical development was compatible with his age; though he seemed rather babyish, his intelligence was felt to be adequate. An EEG carried out one year later was normal. At that time he was still very fidgety and irritable. A psychological examination was suggested, but could not be carried out.

Diagnosis: behaviour difficulties.

No. 75 (401/3/1947)

A boy born in a private clinic at term on Aug. 31 1947 to a primipara following a normal pregnancy. The delivery was prolonged, but apparently uncomplicated. No information is available concerning labour stimulation or morphia. BW was 4200 g. The cord was wound around the infant's neck, and he was asphyxiated for about 20 minutes, during which time he was given oxygen, artificial respiration, lobeline and cardiazol. He developed a generalized clonic convulsion and was immediately transferred to the DPGo with a diagnosis of tentorial tear. On admission he was *rigid*, and during the first 3 days of life he had several convulsions. His muscle tone gradually returned to normal and no other abnormal features were observed. He was discharged after 18 days in apparently good condition.

Diagnosis: intracranial haemorrhage.

His growth and motor development were good: he sat up at 6 months and walked

at 14 months. His motor pattern was normal but he was lefthanded, (so was a half uncle). He had a squint, but his vision was good. He talked at about 2 years. His mental development was fairly satisfactory except for a difficult temperament particularly during his early years of life. He started school at the usual time, but had reading difficulties. During his second year in school the school-psychologist reported his intelligence to be normal. In the third year he was referred to a special reading class. He changed school three times during this year and the following one because of poor progress. From his 12th to 14th year he attended the Institute for Dyslectics. He gradually achieved good standard of reading, but still had trouble with writing. (The half-uncle mentioned above also was dyslectic).—He had nocturnal enuresis until the age of 10 years. (This was not a familial feature).

On follow-up examination, when 11 years of age, his physical development was normal for his age and mentally he appeared normal. There was a negligible squint. His motor development was normal apart from his left-handedness. The neurological examination was normal. EEG was not performed.

Diagnoses: familial (?) dyslexia, squint, previous nocturnal enuresis, lefthandedness.

No 76 (664/3/1950)

A boy born in a private clinic at term on Oct. 8, 1950 to a primipara of 35 years, following a normal pregnancy The delivery was very quick, but otherwise seems to have been uneventful. Labour stimulation as well as morphia was given. The infant was *not* asphyxiated. He was admitted to the DPGe 6 days old because of weight loss, the diagnosis being infantile atrophy During the admission he was rather listless and sucked poorly but was otherwise normal. When discharged after 10 days he was still somewhat listless, but otherwise apparently normal

Diagnosis: congenital debility

His growth as well as his motor and mental development were satisfactory He walked normally at the age of one. His vision and hearing were normal He said single words at one year and his speech was adequate by 2 years. After entering kindergarten at age 3 he began to stammer This persisted, and from the age of six he was given speech therapy with some benefit. He started school at the usual time and his progress was good He presented no behavioural problems, though he was easily frightened He suffered from enuresis (non-familial).

He was followed-up at the age of 7 /₁₂ at which time his physical and mental development was compatible with his age. There was a negligible stammer his speech was otherwise normal. The neurological examination was normal. EEG-examination was refused by the parents.

Diagnoses. stammer enuresis.

No 77 (7466/3/1951)

A girl born at home at term on Aug. 6, 1951 to a multipara following a normal pregnancy The delivery was uneventful. It was stimulated by one injection. There is no record of morphia being given. The infant was not asphyxiated. However she was admitted to DPGe during the first 24 hours because of an episode of generalized convulsions. She presented no other abnormalities and was discharged on the following day in apparently good condition.

Diagnosis: congenital debility

Her growth and development were satisfactory She walked at one year Her motor pattern, vision, hearing and speech were all normal. She talked at 2 years. She presented no behaviour problems, though she was said to be nervous and easily frightened and to have a nocturnal enuresis (which was familial) She started school at the normal time and did well.

On follow-up examination, aged 7 /₁₂ her physical development was compatible with her age. Mental development appeared normal. The neurological examination was normal

Diagnosis. nocturnal enuresis (familial).

No. 78 (2269/3/1953)

A boy born at home at term on May 5, 1953 to a multipara, following normal pregnancy. The delivery was uncomplicated, labour stimulation and morphia were not given, but the delivery took place under full anaesthesia. The infant was asphyxiated for about 20 minutes, during which time he was given lobeline and nikethamide twice. He was immediately admitted to the DPGe with the diagnoses of asphyxia and atelectasis. He was flaccid on admission and during the first day he developed an episode of generalized convulsions. He sucked poorly but recovered after a few days and was discharged after 6 days in apparently good condition.

Diagnoses: congenital debility, nikethamide intoxication.

His growth was good and his mental and physical development satisfactory. He sat up at 7 months and walked at 15 months. His vision and hearing were normal. *He talked before he was two years old. There were no* behaviour problems. He had diurnal and nocturnal enuresis. When just under 5 years old he was admitted to children's hospital (Fuglebakken). No urological abnormalities were found to explain the enuresis. The social conditions were considered unsatisfactory. Psychological testing was not performed. He appeared normally developed.

When seen at *follow-up*, just under 5½ years *of age, his height* was about average, he was well proportioned and well-nourished. His mental development appeared compatible with his age. The neurological examination was normal. An EEG had not been done.

Diagnosis: enuresis.

No. 79 (1667/3/1954)

A boy born in a private clinic at term on April 21 1954, to 32-year-old primipara following a normal pregnancy. The delivery was prolonged, but otherwise apparently normal. There is no report of labour stimulation but morphia was given. BW was 4600 g. The infant was not asphyxiated, but was admitted to the DPGe on the third day with diagnoses *? dehydration and fever.* He was subfebrile on admission (temp. 37.8 C), and he was restless and sucked poorly. His temperature rose to 39.4, but on the same day again fell to 37 C. He gradually sucked better and was discharged after 6 days in apparently good condition except for a doubtful rigidity (his tone had earlier been described as normal).

Diagnoses: intracranial haemorrhage, sequelae of difficult birth.

His growth as well as motor and mental development were satisfactory. He walked at *10* months. *His* vision and hearing were normal. A *divergent* squint was noted. (Similar cases in the family). He talked at 2 years. He presented no real behaviour problems, though he did not get on well with other children, preferring to be on his own, and he amused himself well. There was nocturnal teeth grinding.

At follow-up, when 4½ years of age, he was found to be well-developed physically and mentally. The neurological examination was normal. *He* was not yet dry at night (no family history of enuresis).

Diagnoses: nocturnal enuresis, familial squint.

No. 80 (408 2 1949)

A boy born in private clinic at term on July 15, 1949, to 34-year-old multipara, who during the first three months *of pregnancy* had suffered from severe vomiting and later developed oedema and possibly albuminuria. The membranes had *ruptured some three days* before delivery. Labour-stimulating injections were given (no record of morphia). Otherwise the course was apparently uneventful. BW was 4290 g. Asphyxia was not mentioned in the notes, but nicordamine was given. During the first 24 hours the infant developed cyanotic attacks and was *transferred* to the DPGe suspected of intracranial haemorrhage. He was flaccid and restless on admission, and during the following two days exhibited several additional cyanotic attacks. Thereafter

he improved and presented no further abnormal features. He was discharged after 4 days in apparently good condition.

Diagnosis, suspected intracranial haemorrhage.

His growth as well as his motor and mental development were normal. He walked normally before the age of one year talked at 2 years and started school at the normal time. There were no behaviour problems. He did well at school, but was thought to be dyslectic. However special teaching was not provided by the school. There were other cases of dyslexia in the family

He was seen at follow-up when just under 9 years old. His physical and mental development then was found to be compatible with his age. The neurological examination was normal. EEG had not been performed.

Diagnosis, familial dyslexia (7).

No 81 (3535/3/1952)

A girl born in hospital (St. Lukas Stiftelsen) at term on May 28 1952, to a multipara following a normal pregnancy The delivery was prolonged but otherwise apparently normal. Stimulant injections were given and forceps were applied. Morphia apparently was not given. The infant was asphyxiated for a few minutes, during which time oxygen and lobeline were given. She was transferred to the DPGe within the first 24 hours suspected of intracranial haemorrhage. Her temperature was raised (38 C) On admission she was flaccid, but otherwise normal. Her temperature fell to normal levels within the first 24 hours without any further rise. Her tone gradually became normal. She was discharged after 6 days in apparently good condition.

Diagnoses: intracranial haemorrhage, difficult birth.

Her growth and development were satisfactory She sat and walked early her vision and hearing were normal. She talked before the age of two. She started school when 6 years old and did well. She had had a drooping left eyelid since birth, which persisted unchanged. It was also noted that on exertion the left side of her forehead turned red, while the right side remained pale, with a sharp demarcation line. This prompted referral to the NPO of the RH when she was 4 / years old. The examination revealed no neurological or other abnormalities except for the left sided ptosis. EEG was normal.

She was followed-up at 6 / years. Her physical and mental development then appeared normal. There was a left sided ptosis, otherwise her facial movements were normal. Neurological examination was normal

Diagnosis. left-sided ptosis.

No 82 (6571/3/1951)

A girl born in a private clinic at term on July 19 1951 to a multipara following a normal pregnancy The delivery was prolonged, but apparently otherwise normal. It was stimulated by injection, but morphia was not given. There is no information concerning asphyxia, but lobeline was given. The infant was admitted to the DPGe immediately after birth with a diagnosis of congenital debility suspected heart disease, cyanosis. On admission she was flaccid and cyanotic, and her respiration was grunting. During the first 2 days she sustained repeated cyanotic attacks in spite of oxygen therapy Thereafter she recovered and her respiration and tone gradually returned to normal Chest X ray and auscultation gave no evidence of heart disease. She was discharged after 14 days in apparently good condition.

Diagnosis: atelectasis of the lungs.

Her growth and mental development were satisfactory She walked at one year Her hearing and speech were normal. She had a squint, which was treated by an occlusive eye patch and glasses. The visual acuity of the right eye nevertheless was greatly diminished (No family history of eye defect). Her behaviour was normal and she was expected to be ready for school at the usual time.

At follow-up, at 6¹/ years, she was found to be developed mentally and physically in line with her age. She wore glasses, had mild convergent squint and impaired visual acuity in the right eye. The neurological examination was normal. EEG was not performed.

Diagnosis: convergent squint.

Aa. IJ (3558/205/1955)

A girl born in private clinic before term on May 16, 1955, to a primipara following normal pregnancy. The delivery was accompanied by a good deal of bleeding and slight separation of the placenta was demonstrated. Otherwise the course was normal. There is no record of labour stimulation or morphia. BW was 2300 g. Asphyxia is not recorded. During the first 24 hours the infant was admitted to the DPGs with diagnosis of prematurity congenital debility. On admission she was trembling and her respiration was grunting. During that day she sustained repeated cyanotic attacks. Her respiration improved within 24 hours and she gradually became more quiet. No other abnormal features were observed. She was discharged after 19 days in apparently good condition.

Diagnosis: suspected *intracranial haemorrhage*.

Her growth and physical development were satisfactory. She walked at one year. She had a convergent squint (which was familial feature); her vision was felt to be normal. Her hearing was adequate. She talked at about 18 months. Her mental development and behaviour were satisfactory.

On follow-up examination, aged 3¹/ years, she was found to have developed physically and mentally according to her age. The neurological examination was normal. Her convergent squint persisted.

Diagnosis: (familial) convergent squint.

he improved and presented no further abnormal features. He was discharged after 4 days in apparently good condition.

Diagnosis: suspected intracranial haemorrhage.

His growth as well as his motor and mental development were normal. He walked normally before the age of one year talked at 2 years and started school at the normal time. There were no behaviour problems. He did well at school, but was thought to be dyslectic. However special teaching was not provided by the school. There were other cases of dyslexia in the family

He was seen at follow-up when just under 9 years old. His physical and mental development then was found to be compatible with his age. The neurological examination was normal. EEG had not been performed.

Diagnosis. familial dyslexia (?).

No 81 (3535/3/1952)

A girl born in hospital (St. Lukas Stiftelsen) at term on May 28 1952, to a multipara following a normal pregnancy The delivery was prolonged but otherwise apparently normal. Stimulant injections were given and forceps were applied. Morphia apparently was not given The infant was asphyxiated for a few minutes, during which time oxygen and lobeline were given. She was transferred to the DPGo within the first 24 hours suspected of intracranial haemorrhage. Her temperature was raised (38 C) On admission she was flaccid, but otherwise normal. Her temperature fell to normal levels within the first 24 hours without any further rise. Her tone *gradually became normal. She was discharged after 6 days in apparently good condition*

Diagnoses. intracranial haemorrhage, difficult birth.

Her growth and development were satisfactory She sat and walked early her *vision and hearing were normal. She talked before the age of two. She started school* when 6 years old and did well. She had had a drooping left eyelid since birth, which persisted unchanged. It was also noted that on exertion the left side of her forehead turned red, while the right side remained pale, with a sharp demarcation line. This prompted referral to the NPO of the RH when she was 4 / years old. The examination revealed no neurological or other abnormalities except for the left sided ptosis. EEG was normal.

She was followed-up at 6¹/ years. Her physical and mental development then appeared normal. There was a left sided ptosis, otherwise her facial movements were normal. Neurological examination was normal.

Diagnosis: left sided ptosis.

No 82 (6571/3/1951)

A girl born in a private clinic at term on July 19 1951 to a multipara following a normal pregnancy The delivery was prolonged, but apparently otherwise normal. It was stimulated by injection, but morphia was not given. There is no information concerning asphyxia, but lobeline was given. The infant was admitted to the DPGe immediately after birth with a *diagnosis* of congenital *debility* suspected heart disease, cyanosis. On admission she was flaccid, and cyanotic, and her respiration was grunting. During the first 2 days she sustained repeated cyanotic attacks in spite of oxygen therapy Thereafter she recovered and her respiration and tone gradually returned to normal. Chest X ray *and auscultation gave no evidence of heart disease.* She was discharged after 14 days in apparently good condition.

Diagnosis: atelectasis of the lungs.

Her growth and mental development were satisfactory She walked at one year Her hearing and speech were normal. She had a squint, which was treated by an occlusive eye patch and glasses. The visual acuity of the right eye nevertheless was greatly diminished. (No family history of eye defect). Her behaviour was normal and she was expected to be ready for school at the usual time.

References

Ahvenainen, E. K. Acute subdural hematoma of the newborn. *Ann. Paediat. Fenn.* 1956, 2 111. (16, 66).

Ahvenainen, E. K. Clinical symptoms of respiratory disorders in newborns I. *Ann. Paediat. Fenn.* 1957 3 1. (16, 66).

Ahvenainen, E. K. *Clinical symptoms of respiratory* disorders in the newborn III. *Ann. Paediat. Fenn.* 1958, 4 161. (16, 66).

Ahvenainen, E. K. Clinical symptoms of respiratory disorders in the newborn VI. *Ann. Paediat. Fenn.* 1959 5 98. (16, 66).

Alm, L. The long-term prognosis for prematurely born children. *Acta paediat (Uppsala)* 1953, suppl. 94. (101, 105).

André-Thomas & S. Saint-Anne Dargassies: *Etudes Neurologiques sur le Nouveau-Né et le Jeune Nourrison*, Paris: Masson et C^ie^ Olivier Perrin 1952. (22).

Apgar, V A Proposal for New Method of Evaluation of the Newborn Infant. *Anesth. et Analg* 1953 32 260. (21).

Asher P & F E. Schonell. A Survey of 400 Cases of Cerebral Palsy in Childhood. *Arch. Dis. Childh.* 1950, 25 360. (48, 101).

Aurup, R. *Fødselstraumer anoxi og hjerneskadersdelse hos børn.* Nord. Med. 1959 62 1303 (53).

d'Avignon, M & S. Kalson: Electroencephalographic Findings in Children, Previously Treated for Asphyxia Neonat. *Acta paediat.* (*Uppsala*) 1953 42 407 (57).

Bakwin, H Cerebral Damage and Behavior Disorders in Children. *J Pediat.* 1949 34 371 (51).

Bamberger P & A. Matthes: *Anfälle im Kindesalter* Basel: S. Karger 1959 p. 369 (50), p. 206 (51) and p. 379 (51).

Barclay I A Survey of Cerebral Palsy in Otago. *N Z med J* 1956, 55 199 (49 95, 101).

Belnap, W D., C. P McKhann & C. S. Beck: Cerebral birth injury in retrospect. *J Pediat* 1950, 37 326 (48).

Benaron, H B. W M. Brown, B. E. Tucker V Wentz & G. K. Yacorzynski: The remote effects of prolonged labor with forceps delivery precipitate labor with spontaneous delivery and natural labor with spontaneous delivery on the child. *Amer J Obstet Gynec* 1953 66 551 (96).

Benaron, H. B. W R. E. Tucker J P Andrews, B. Boshes, J Cohen, E. Fromm & G. K. Yacorzynski: Effect of anoxia during labor and immediately after birth on subsequent development of the child. *Amer J Obstet. Gynec.* 1960, 80 1129 (97 98).

Benda, C. E. & G. P Hoessly: Postnatal and Natal Cerebral Injuries. *Arch. Neurol. Psychiat.* 1956, 76 236. (49).

Bender L. *Organic brain conditions producing behavior disturbances.* In: N D. C. Lewis & B. L. Pacella (Eds.): Modern trends in child psychiatry New York: Int. Univ Press, 1945. (51).

References

Ahvenainen, E. K. Acute subdural hematoma of the newborn. *Ann. Paediat. Fenn.* 1956, 2 111. (16, 66).

Ahvenainen, E. K. Clinical symptoms of respiratory disorders in newborns I. *Ann. Paediat. Fenn.* 1957 3 1 (16, 66).

Ahvenainen, E. K. Clinical symptoms of respiratory disorders in the newborn III. *Ann. Paediat. Fenn.* 1958, 4 161. (16, 66).

Ahvenainen, E. K. Clinical symptoms of respiratory disorders in the newborn VI. *Ann. Paediat. Fenn.* 1959 5 98. (16, 66).

Alm, I. The long-term prognosis for prematurely born children. *Acta paediat (Uppsala)* 1953 suppl. 94 (101, 105).

André-Thomas & S. Saint Anne Dargassies: *Études Neurologiques sur le Nouveau-Né et le Jeune Nourrisson*, Paris: Masson et C^ie Olivier Perrin 1952. (22).

Apgar V A Proposal for New Method of Evaluation of the Newborn Infant. *Anesth. Analg* 1953 32 260. (21).

Asher, P & F E. Schonell: A Survey of 400 Cases of Cerebral Palsy in Childhood. *Arch Dis Childh.* 1950, 25 360. (48, 101).

Astrup, R. *Fødselstraumer ... og hjerneskader hos børn.* Nord. Med. 1959 62 1303 (53).

d'Avignon, M. & S. Kellson: Electroencephalographic Findings in Children, Previously Treated for Asphyxia Neonat. *Acta paediat. (Uppsala)* 1953, 42 : 407 (57).

Bakwin, H Cerebral Damage and Behavior Disorders in Children. *J Pediat.* 1949 34 371 (51).

Bamberger P & A. Matthes: *Anfälle im Kindesalter* Basel: S. Karger 1959 p. 369 (50), p. 206 (51) and p. 379 (51).

Barclay J A Survey of Cerebral Palsy in Otago. *N Z. med. J* 1956, 55 199 (49 95, 101).

Belamp, W D., C. F McKhann & C. S. Beck: Cerebral birth injury in retrospect. *J Pediat* 1950, 37 326. (48)

Benaron, H. B. W M. Brown, B E. Tucker V Wentz & G. K. Yacorzynski: The remote effects of prolonged labor with forceps delivery precipitate labor with spontaneous delivery and natural labor with spontaneous delivery on the child. *Amer J Obstet Gynec* 1953 66 551 (96).

Benaron, H. B W B. E. Tucker J P Andrews, B. Boshes, J Cohen, E. Fromm & G. K. Yacorzynski: Effect of anoxia during labor and immediately after birth on subsequent development of the child. *Amer J Obstet. Gynec.* 1960, 80 1129 (97 98).

Benda, C E. & G. F Hoessly Postnatal and Natal Cerebral Injuries. *Arch. Neurol. Psychiat.* 1956, 76 236. (49).

Bender L. *Organic brain conditions producing behavior disturbances.* In: N. D C. Lewis & B. L. Pacella (Eds.): Modern trends in child psychiatry New York: Int. Univ Press, 1945 (51).

Beskow B. Mental Disturbances in Premature Children at School Age. *Acta pædiat. (Uppsala)* 1949 37 125 (102, 105).
Blegen, S. D The premature child *Acta pædiat (Uppsala)* 1953 42. suppl. 88 378. (101 102).
Bound, J P N R. Butler & W G Spector Classification and Causes of Perinatal Mortality *Brit med. J* 1956, 2 1191 and 1260 (15 71 66).
Brady J M Lumbar Puncture in Meningeal Hemorrhage of the Newborn. *J Amer med. Ass* 1918 71 347 (13 17).
Brandt, H S. Brandt & K. Vollmond EEG Response to Photic Stimulation in 120 Normal Children. *Epilepsia* 1961 2 313 (57).
Bridge, E. M. *Epilepsy and Convulsive Dsorders in Children* New York: McGraw-Hill Book Comp. Inc. 1949 p. 254 (53), p. 115 (49), p. 49 (50).
Buch, N H. The Inner Ear of Newborn Infants. *J Laryng* 1966, 80 765 (52).
Burke, J B. The prognostic significance of neonatal convulsions. *Arch. Dis Childh.* 1954 29 342. (70).
Campbell, W A. B., E. A. Cheeseman & A. W Kilpatrick. The Effects of Neonatal Asphyxia on Physical and Mental Development. *Arch Dis. Childh. 1950,* 25 351 (97).
Capper A. The Fate and Development of the Immature and of the Premature Child. *Amer J Dis Child.* 1928, 35 262 og 443 (102).
Catel, W Zur klinischen Diagnose intrakranieller Geburtsblutungen. *Mschr Kinderheilk* 1932, 52 1 (14).
Catel, W.. Uber das spätere Schicksal von Kindern mit intrakraniellen Geburtsblutungen. *Mschr Kinderheilk* 1933 58 89 (18).
Clein, N W. Premature Infants. *Amer J Dis Child* 1929 37 751 (13 66).
Comberg, M.. Über Schicksal und Entwicklung von Frühgeborenen bis zum Spiel- und frühen Schulalter *Z. Kinderheilk.* 1927 43 462. (102, 105).
Craig, W S. Intracranial Haemorrhage in the New-born. *Arch. Dis Childh.* 1938, 13 89 (14).
Craig, W S.. Intracranial Irritation in the Newborn. Immediate and Long Term Prognosis. *Arch. Dis Childh.* 1950 25 325 (19).
Craig, W S.. Convulsive Movements Occuring in the First 10 Days of Life. *Arch. Dis Child* 1960, 35 336. (16, 21 66).
Craigie, E. H The comparative anatomy and embryology of the capillary bed of the central nervous system. *Res. Publ Ass. nerv ment Dis.* 1938 18 3 (52).
Creak, M Reading Difficulties in Children. *Arch Dis. Childh.* 1936, 11 143 (54).
Critchley Macdonald. *Developmental Dyslexia* London. Heinemann Medical Books Ltd. 1964 p. 17 (55).
Crothers, B. & R. S. Paine: *The Natural History of Cerebral Palsy* Cambridge, Mass. Harvard Univ Press 1959 p. 64 (48).
Dann, M., S. Z. Levine & E. V New The Development of Prematurely Born Children with Birth Weights or Minimal Postnatal Weights of 1000 grams or Less. *Pediatrics.* 1958 22 1037 (101 102).
Dann, M., S. Z. Levine & E. V New A Long Term Follow-up Study of Small Premature Infants. *Pedatrics* 1964, 33 945 (101).
Darke, R. A. Late Effects of Severe Asphyxia Neonatorum. *J Pediat* 1944, 24 148. (98).
Davey P R Hearing Loss in Children of Low Birth Weight. *J Laryng* 1962, 76 274 (53).
Dekaban, A.. *Neurology of Infancy* Baltimore: The Williams & Wilkins Comp. 1959 p. 66–76 (16) and 77–79 (99).
Denhoff, E. & R. H. Holden. Pediatric Aspect of Cerebral Palsy *J Pediat* 1951 39 363 (101).
Dijkstra, J *The prognostic value of the neurological examination of the newborn.* Thesis. Univ Groningen, Holland. 1960 (22).

Dollinger A., Geburtstrauma und Zentralnervensystem. *Ergebn. inn. Med. Kinderheilk.* 1927 31 373. (13, 17).

Donovan, D. E., P Coues & R. S. Paine: The prognostic implications of neurological abnormalities in the neonatal period. *Neurology (Minneap.)* 1962, 12 910. (22).

Douglas, A. A.: The Eyes and Vision in Infantile Cerebral Palsy *Trans. ophthal. Soc. U K.* 1961, 80 311 (56).

Drage, J. S., C. Kennedy & B. K. Schwartz: The Apgar Score as an Index of Neonatal Mortality *Obstet. and Gynec.* 1964, 24 222. (21).

Drage, J. S. & H. Berendes: Apgar Scores and Outcome of the Newborn. *Pediat. Clin. N Amer* 1966, 13 635 (22).

Drew A. L.: A Neurological Appraisal of Familial Congenital Word-Blindness. *Brain* 1956, 79: 440. (54).

Drillien, C. M.: Physical and Mental Handicap in the Prematurely Born. *J Obstet Gynaec. Brit. Emp* 1959 66 721. (101 102, 105).

Drillien, C. M. A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. IV *Arch. Dis. Childh.* 1959 34 210. (102).

Drillien, C. M.: The Incidence of Mental and Physical Handicaps in School-age Children of Very Low Birth Weight. *Pediatrics.* 1961, 27 452. (102).

Drillien, C. M. A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children VII. *Arch. Dis. Childh.* 1961 36 233 (101).

Drillien, C. M., T T S. Ingram & E. M. Russell. Comparative Aetiological Studies of Congenital Diplegia in Scotland. *Arch. Dis. Childh.* 1962, 37 282. (95).

Drillien, C. M S. Jameson & E. M. Wilkinson: Studies in Mental Handicap I. *Arch. Dis. Childh.* 1966, 41 528 (49).

Dunning, H. S. & H. G Wolff: Relative vascularity of various parts of central and peripheral nervous system of cat and its relation to function. *J comp. Neurol.* 1937 67 433 (52).

Eames, T H.. Reading Failures and Nonfailures in Children with Brain Damage. *Amer J Ophthal.* 1959 47 74. (54).

Eastman, N. J & M. DeLeon: The Etiology of Cerebral Palsy *Amer J Obstet. Gynec* 1955, 69 950. (48).

Eastman, N. J S. O. Kohl, J E. Maisel & F Kavaler: Obstetrical Background of 753 Cerebral Palsy Cases. *Obstet gynec. Surv* 1962, 17 459 (49).

Eichhart, C R., F K. Graham & D L. Thurston: The relationship of perinatal anoxia to intelligence and to neurological deviations in the preschool child. *Presented to The American Psychological Association* 1958. (98).

Esch, P Zur Klinik und Therapie der intrakraniellen Blutungen beim Neugeborenen. *Zbl. Gynäk.* 1916, 40 321 (13 66).

Ettinger G. & L. Hurwitz: Dyslexia and its associated disturbances. *Neurology* 1962, 12 478. (54).

Eustis, R. S.. The primary etiology of the specific language disabilities. *J Pediat.* 1947 31 448. (54).

Fisch, L. & D. A. Osborn: Congenital Deafness and Haemolytic Disease of the Newborn. *Arch Dis. Childh.* 1954, 29 309 (52).

Fisch, L.. *The Aetiology of Congenital Deafness and Audiometric Patterns. J Laryng.* 1955 69 479 (53).

Fischer E. Über das spätere Schicksal von Kindern mit geburtstraumatischen Krämpfen *Münch med Wschr* 1938, 85 1582. (18).

Fleming, G B. & E. D. Morton: Meningeal Haemorrhage in the Newborn. *Arch. Dis. Childh* 1930, 5 361 (18).

Flottorp, G D E. Morley & M. Skatvedt: The localization of hearing impairment in athetoids. *Acta oto-lary g (Stockh.)* 1957 48 404. (53).

Ford, F R *Diseases of the Nervous System in Infancy Childhood and Adolescence.* Springfield, Illinois: Charles C Thomas Publ. 1960, p. 1040 (21), 258 (55).

Franklin, A. D *Occurrence* J *Spular* Copenhagen 1960, p. 27 and 108 (56).

Fraser M S. & J Wilks. The Residual Effects of Neonatal Asphyxia. *J Obstet. Gynaec. Brit Emp* 1959 **66** 748. (98).
Friderichsen, C. & J Melchior Febrile Convulsions in Children Their Frequency and Prognosis. *Acta pædiat (Uppsala)* 1954, **43** 307 (50).
Friedländer A. Einige Ausführungen über Klinik und Prognose des frühgeborenen Kindes. *Acta pædiat (Uppsala)* 1934 **17** suppl. I 110 (102).
Frisk, M., R. L. Takkunen & G Holmström. Small Prematures at 6–7 Years of Age III. *Ann. Paediat Fenn.* 1964 **10** 79 (101 102).
Fuldner R. V.. Labor Complications and Cerebral Palsy *Am. J Obstet. Gynec* 1957 **74** 159 (101).
Gallagher J R.. Specific Language Disability *New Engl. J Med* 1950 **242** 436. (54).
Gesell, A. & C. S. Amatruda. *Developmental Diagnosis*. New York. Hoeber 1947 p. 246. (54).
Gottlieb J S., J R. Knott & M. C. Ashby Electroencephalographic Evaluation of Primary Behaviour Disorders in Children. *Arch. Neurol. Psychiat* 1945 **53** 138. (52).
Graham, F K., R. G Matarazzo & B M. Caldwell. Behavioral Differences Between Normal and Traumatized Newborns. *Psychol. Monogr* 1956, **70** 1 (22).
Graham, F K., C. B. Ernhart & D Thurston: The Relationship of Neonatal Apnea to Development at Three Years. *Mental Retardation* 1962, **39** 159 (98).
Graham, F K., C. B Ernhart, D Thurston & M. Craft. Development Three Years After Perinatal Anoxia and Other Potentially Damaging Newborn Experiences. *Psychol. Monogr* 1962, **76** 1 (22, 99).
Green, R. M. Intracranial Haemorrhage in the Newborn. *Boston med surg J* 1914 **170** 682. (12).
Gross, H.. Nachuntersuchungen von Kindern, die in der Neugeborenenperiode einer perinatalen Schädigung boten. *Neue öst Z. Kinderheilk* 1958, **3** 195 (20).
Grulee, C. G Intracranial Haemorrhage of the Newborn. *Am. J Dis. Child.* 1936, **52** 648. (14 66).
Gulbor G P Some Eye Defects seen in Cerebral Palsy *Amer J phys. Med* 1953 **32** 342. (56).
Hall, J G On the Neuropathological Changes in the Central Nervous System Following Neonatal Asphyxia. *Acta otolaryng (Stockh)* 1963 suppl. **188** 331 (52).
Hall J G The Auditory Pathway in Neonatal Asphyxia. Proc. V[th] Internat. Congr Neuropath. 1965 *Excerpta med Internat. Congr Series (Amst)* 1966, no. **100** 906. (52).
Hallgren B Specific Dyslexia. *Acta psychiat scand* 1950 suppl. 65 (54).
Harlem, O K. & S. Oseid. Prognosis of Cerebral Birth Injury *Acta pædiat (Uppsala)*. 1961–63 suppl. **140** 72. (21).
Harper P A., L. K. Fischer & R. V Rider Neurological and Intellectual Status of Prematures at Three to Five Years of Age. *J Pediat.* 1959 **55** 679 (102).
Heidler H. Aut laesio intracranialis aut asphyxia neonatorum? *Z. Geburtsh. Gynäk* 1927 **91** 235 (13 17 66).
Heimer C. B., R. Cutler & A. M. Freedman: Neurological Sequelae of Premature Birth. *Am J Dis Child.* 1964 **108** 122. (102)
Hellström, B & B. Jonsson. Late prognosis in asphyxia neonatorum. *Acta pædiat (Uppsala)* 1953 **42** 398 (20).
Hermann, K.. *Om medfødt ordblindhed* Copenhagen. Munksgaard 1955 p. 112. (54).
Hermann, K. *Reading Disability* Copenhagen 1959 (54).
Hess, J H., G J Mohr & P F Bartelem. *The Physical and Mental Growth of Prematurely Born Children.* Chicago: Univ Chicago Press 1934 (102, 105).
Hess, J H Experiences Gained in a Thirty Year Study of Prematurely Born Infants. *Pediatrics* 1953 **11** 425 (102).
Hinshelwood, J *Congenital Word Blindness.* London: H K. Lewis 1917 (54).
Horstmann, W & W Schinnerling: Zur Prognose der sogenannten Fieberkrämpfe. *Mschr Kinderheilk* 1963 **111** 52. (51).

Hater K. A. Über Beziehungen zwischen intra- und postnataler Hypoxie sowie zerebralen Spätschäden beim Kind. *Geburtsh. u. Frauenheilk.* 1962, 22 846. (97 99).
Illingworth, R. S. The After History of Premature Infants. *Arch. Dis. Childh.* 1939 14 121 (101, 102).
Illingworth, R. S. Cyanotic Attacks in Newborn Infants. *Arch. Dis. Childh.* 1957 32 328. (15, 66).
Illingworth, R. S. Difficulties in Developmental Prediction. *Little Club Clin. Develop. Med.* 1960, 2 58. (22).
Ingram, T T S. A characteristic form of overactive behavior in brain damaged children. *J ment. Sci.* 1956, 102 550. (51).
Jasper, H. H., P Solomon & C. Bradley Electroencephalographic Analyses of Behavior Problem Children. *Amer J Psychiat* 1938, 95 641. (51).
Johnsen, S. *Period nervøsitet hos born.* Copenhagen 1954, p. 40. (53).
Kawi, A. R. & B. Pasamanick. Prenatal and Paranatal Factors in the Development of Childhood Reading Disorders. *Monogr Soc Res. Child. Dev* 1959 24 1. (55).
Keith, H. M., M. A. Norval & Hunt: Neurological Lesions in Relation to Sequelae of Birth Injury *Neurology* 1953, 3 139 (96).
Keith, H. M. & R. P Gage: Neurological Lesions in Relation to Asphyxia of the Newborn and Factors of Pregnancy *Pediatrics.* 1960, 26 616. (96).
Kennard, M. A. & M. D. Willner The Significance of Paroxysmal Patterns in Electroencephalograms of Children Without Clinical Epilepsy *Res. Pub Ass. nerv ment. Dis.* 1947 26: 308. (52).
Knobloch, H., R. Rider P Harper & B. Pasamanick: Neuropsychiatric Sequelae of Prematurity *J Amer med. Ass.* 1956, 161 581 (101 102).
Kremer, H. & G Nack. Spätfolgen im Sinne geistiger Entwicklungsstörungen bei Zangen- und Spontangeburten. *Münch. med. Wschr* 1957 99 321 (97).
Kern, T Studier over den perinatale dødelighed I. *Bibl. læger* 1955 147 1. (91).
Larsen, E. J A Neurologic-etiologic Study on 1000 Mental Defectives. *Acta psychiat. scand.* 1931 6 37 (49).
Laufer, M. W & E. Denhoff: Hyperkinetic Behavior Syndrome in Children. *J Pediat.* 1957 50 463 (51).
Lampp, R. Die Bedeutung der frühkindlichen Hirnschädigung für die Neurose im Kindesalter *Acta paedopsychiat.* 1964, 31 152. (51).
Levy P H. & H. Kobrak: *Arch. Neurol. Psychiat.* 1936, 35 839 (52).
Liebe, S. Zur Diagnose und Prognose geburtstraumatischer intrakranieller Blutungen. *Mschr Kinderheilk.* 1940, 83 1 (14, 18, 66).
Lilienfeld, A. M. & E. Parkhurst: A Study of the Association of Factors of Pregnancy and Parturition with the Development of Cerebral Palsy *Amer J Hyg.* 1951 53 262. (48).
Livingston, S. *The Diagnosis and Treatment of Convulsive Disorders in Children.* Springfield, Illinois: Charles C Thomas Publ. 1954, p. 24. (50).
Lubchenco, L. O., P A. Horner L. H. Reed, I. E. Hix, J D. Metcalf, R. Cohig, H. C. Elliott & M Bourg: Sequelae of Premature Birth. *Am. J Dis. Child.* 1963 106 101 (101 102).
Malmquist, E. *Factors Related to Reading Disabilities in the First Grade of Elementary School* Stockholm: Almqvist & Wiksell 1958, p. 243. (54).
Mann, A. G D. The Causes of Deafness in Childhood. *J Laryng* 1966, 80 495. (53).
Marstrander J En prospektiv studie over den psykomotoriske utvikling hos prematurt barn med fødselsvekt under 2000 g. *Utensk. A bejder Sentralrast. Cerebral Parese.* Oslo 1964, p 35 (101, 102).
McDonald, A. D Cerebral Palsy in Children of Very Low Birth Weight. *Arch. Dis. Childh.* 1963 38 579 (102).
McDonald, A. D Deafness in Children of Very Low Birth Weight. *Arch. Dis. Childh.* 1964, 39 272. (53).
McNeil, N L. *Brit. J Ophthal.* 1955, 39 688. (56).
McNutt, S. Apoplexia Neonatorum. *Amer J Obstet.* 1885, 18 73 (12).

McPhail, F L. & E. L. Hall. Consideration of Cause and Possible Late Effect of Anoxia in the Newborn Infant. *Amer J Obstet Gynec* 1941 42 686. (97).
Millar J H. D Epilepsy and Strabismus. *Epilepsia* 1965 6 43 (56).
Munro, D & R. S. Eustis: The Diagnosis and Treatment of Intercranial Hemorrhage in the Newborn. *Am J Dis Child* 1922, 24 273 (13).
Munro, D Cranial and Intracranial Damage in the Newborn. *Surg Gynec. Obstet* 1928, 47 622. (17).
Munro, D Symptomatology and Immediate Treatment of Cranial and Intracranial Injury in the Newborn, Including Intracranial Hemorrhage. *New Engl J Med.* 1930, 203 502. (17).
Mörstad, O & B R. Kaada. Electroencephalographic Studies of Infants and Children who Acquired Intracranial Injuries at Birth. *Neurology (Minneap.)* 1953 3 544 (57).
Naujoks, H. Das spätere Schicksal der Kinder mit intrakraniellen Geburtsläsionen. *Mschr Geburtsh. Genak.* 1928, 80 297 (17).
Nicholls, J V V Congenital Dyslexia. A Problem in Etiology *Canad. med Ass. J* 1960 82 575 (54).
Nicholls, J V V.. Reading Difficulties in Children. *Int Ophthal Clin* 1965 5 423 (54).
Nielsen, H H *A Psychological Study of Cerebral Palsied Children.* Copenhagen. Munksgaard 1966. (51).
Nielsen, J M. & C. B. Courville: Role of Birth Injury and Asphyxia in Idiopatic Epilepsy *Neurology* 1951 1 48. (50).
Orton, S. T.. *Arch Neurol Psychiat* 1925 14 581 (54).
Orton S. T *Reading Writing and Speech Problems in Children.* London: Chapman & Hall 1937 p. 200. (54).
Pache, H D Die Klinik der kindlichen Krampfleiden. *Mschr Kinderheilk* 1954 102 42. (49).
Paine, R. S. The Immediate Value of the Neonatal Neurological Examination. *Little Club Clin Develop. Med* 1960 2 62. (22).
Pasamanick, B. & A. M Lilienfeld Association of Maternal and Fetal Factors with Development of Mental Deficiency *J Amer med. Ass* 1955 159 155 (49).
Pasamanick, B & A. M. Lilienfeld. Maternal and Fetal Factors in the Development of Epilepsy *Neurology* 1955 5 77 (50)
Peiffer J Morphologische Aspekte der Epilepsien. *Monogr gesamt Neurol. Psychiat* 1963 100 p. 127 (51).
Perlstein M.A E. L. Gibbs & F A. Gibbs. The electroencephalogram in infantile cerebral palsy *Res Publ. Ass nerv ment Dis* 1947 26 377 (57).
Perlstein, M. A. & H. E. Barnett: Nature and Recognition of Cerebral Palsy in Infancy *J Amer med Ass* 1952, 148 1389 (50).
Peterman, M. G Convulsions in Childhood. *Amer J Dis Child.* 1946, 72 399 (16, 50 66).
Peterman, M. G Febrile Convulsions. *J Pediat* 1952, 41 537 (51).
Plum, P Cerebral Palsy *Dan med. Bull* 1956, 3 99 (48, 50, 56, 95 101).
Polaček L. J Vajporsky & S. Novák. EEG in Healthy Children Aged Six and Six and a Half Years. *Česk Pediat Praha* 1965 20 946. (57).
Prechtl, H F R. Die Entwicklung und Eigenart frühkindlicher Bewegungsweisen. *Klin. Wschr* 1956, 34 281 (22).
Prechtl, H F R. & J Dijkstra. *Neurological Diagnosis of Cerebral Injury in the Newborn* In. Proc. Sympos. Prenatal Care. Noordhoff Groningen. ed. B. S. ten Berge 1959 (22).
Prechtl H. F R The Long-term Value of the Neurological Examination of the New born Infant. *Little Club Clin. Develop. Med* 1960, 2 69 (22).
Prechtl, H F R *Reading Difficulties as a Neurological Problem in Childhood* In: J Money *Reading Disability* Baltimore: The Johns Hopkins Press 1962, p. 187

Prechtl, H. F. R. & D. Beintema. The Neurological Examination of the Full Term Infant. *Little Club Clin. Develop. Med.* 1964, no. 12. (22).
Preston, M.: Late Behavioral Aspects Found in Cases of Prenatal, Natal and Postnatal Anoxia. *J Pediat.* 1945, 26 353 (51).
Rabinovitch, R. D A. L. Drew R. N. De Jong, W Ingram & L. Withey: A Research Approach to Reading Retardation. *Res. Publ. Ass. Res. nerv ment Dis.* 1954, 34 363. (54).
Reinhold, M. The Effect of Laterality on Reading and Writing. *Proc roy Soc. Med.* 1963 56 203 (54).
Robon, P Etiology of Congenital Cerebral Palsy *Arch. Pediat.* 1962, 79 233 (49 95).
Rogers, M. & A. Lilienfeld: Prenatal and Paranatal Factors in the Development of Childhood Behavior Disorders. *Acta psychiat. scand.* 1955 suppl. 102. (51).
Rosenfeld, G. B. & C. Bradley: Childhood Behavior Sequelae of Asphyxia in Infancy *Pediatrics.* 1948, 2 : 74. (51).
Rosier, A.: The Future of the Premature Infant. *Develop. Med. Child. Neurol.* 1962, 4 483. (102).
Roudinesco, J G Tardieu, M. Barawillwald & J Trelat. Étude de 62 cas de lésions cerebro-meningées suivies au cours de la première enfance. *Arch. Franç Pédiat* 1951 8 136. (19).
Russ, J D R. Strong & P Christian: Asphyxia of the newborn infant. *Amer J Obstet Gynec.* 1946, 51 643. (97).
Rydberg, E. Cerebral injury in the new-born children consequent on birth-trauma. *Acta path. microbiol. scand.* 1932, suppl. 10, p. 108 and 127 (14), 140 (18) and 146 (56).
Saint-Anne Dargassies, S. Le nouveau-né à terme: Aspect neurologique. *Biol. Neonat* (Basel) 1962, 4 174. (22).
Schlange, H. Elektroencephalographische Befunde bei Kindern mit Verhaltensstorungen. *Arch. Kinderheilk.* 1963 169 123 (52)
Seitz, L. Ueber Hirndrucksymptome bei Neugeborenen in Folge intrakranieller Blutungen und mechanischer Hirninsulte. *Arch. Gynäk.* 1907 82 528. (12, 66).
Sefbury J B. The Importance of Lumbar Puncture in Intracranial Hemorrhage f the New-Born. *Arch. Pediat.* 1920, 37 545. (13).
Silagy J L. Séquelles psycho-motrices et électroencéphalographiques des hémorragies cérébro-méningées et oedèmes cérébraux des débiles et des prématurés. *Strasbourg méd.* 1965 16 149 (102, 105).
Silver A. Behavioral Syndroms Associated with Brain Damage in Children. *Pediat. Clin. N Amer* 1958, 5 687 (51).
Skatvolt, M. *Cerebral Palsy* Oslo: Oslo University Press 1958, p. 11 (49 95), p. 13 (101).
Skydsgaard, H. B *Den konstitutionelle Dyslexi.* Copenhagen. Nyt Nordisk Forlag 1942. (54).
Smith, R. C Robinson & W G Lennox: Acquired Epilepsy *Neurology* 1954, 4 19 (50).
Smithells, R. W Prognostic Value of Neurological Examinations in the Newborn. *Cerebr Palsy Bull.* 1961 3 7 (22).
Stechler G A Longitudinal Follow-up of Neonatal Apnea. *Child Development.* 1964, 35 333 (98)
Sullerman, M L. E. L. Gibbs & M. A. Perlstein: Electroencephalographic Changes in Strabismus. *Amer J Ophthal* 1952, 35 54. (57).
Sonde, A Die Prognose der Fruhgeborenen und die Prophylaxe des Geburtstraumas. *Act obstet. gynec scand.* 1930, 9 475. (101 102).
Thom, D A. Convulsions of early life and their relation to the chronic convulsive disorders and mental defects. *Amer J Psychiat.* 1942, 98 574. (49).
Thomsen, E. Some considerations regarding the aetiology the incidence and the course of concomitant strabismus. *Trans. ophthal. Soc. U K.* 1964, 44 238. (56).

McPhail, F L. & E. L. Hall. Consideration of Cause and Possible Late Effect of Anoxia in the Newborn Infant. *Amer J Obstet Gynec* 1941 42 686. (97).

Miller J H. D Epilepsy and Strabismus. *Epilepsia* 1965 6 43 (56).

Munro, D & R. S. Eustis: The Diagnosis and Treatment of Intercranial Hemorrhage in the Newborn. *Am. J Dis. Child* 1922, 24 273 (13).

Munro, D Cranial and Intracranial Damage in the Newborn. *Surg Gynec Obstet.* 1928, 47 622. (17).

Munro, D Symptomatology and Immediate Treatment of Cranial and Intracranial Injury in the Newborn, Including Intracranial Hemorrhage. *New Engl J Med.* 1930, 203 502. (17).

Mörstad, O & B R. Kaada. Electroencephalographic Studies of Infants and Children who Acquired Intracranial Injuries at Birth *Neurology (Minneap)* 1953 3 544 (57).

Naujoks, H Das spätere Schicksal der Kinder mit intrakraniellen Geburtsläsionen. *Mschr Geburtsh. Gendk* 1928, 80 297 (17).

Nicholls, J V V Congenital Dyslexia. A Problem in Etiology *Canad med Ass. J* 1960 82 575 (54).

Nicholls, J V V Reading Difficulties in Children. *Int Ophthal. Clin.* 1965 5 423 (54).

Nielsen, H. H. *A Psychological Study of Cerebral Palsied Children* Copenhagen. Munksgaard 1966 (51).

Nielsen, J M & C. B. Courville: Role of Birth Injury and Asphyxia in Idiopatic Epilepsy *Neurology* 1951 1 48 (50).

Orton, S. T.. *Arch. Neurol Psychiat* 1925 14 581 (54).

Orton, S. T *Reading Writing and Speech Problems in Children* London. Chapman & Hall 1937 p. 00. (54).

Pache, H D Die Klinik der kindlichen Krampfleiden. *Mschr Kinderheilk* 1954 102 42. (49).

Paine, R. S The Immediate Value of the Neonatal Neurological Examination. *Little Club Clin Develop Med* 1960 2 62. (22)

Pasamanick, B. & A. M Lilienfeld. Association of Maternal and Fetal Factors with Development of Mental Deficiency *J Amer med. Ass* 1955 159 155 (49).

Pasamanick, B. & A. M. Lilienfeld. Maternal and Fetal Factors in the Development of Epilepsy *Neurology* 1955 5 77 (50).

Peiffer J Morphologische Aspekte der Epilepsien. *Monogr gesamt Neurol. Psychiat* 1963 100 p. 127 (51).

Perlstein, M.A., E. L. Gibbs & F A. Gibbs. The electroencephalogram in infantile cerebral palsy *Res Publ. Ass nerv ment. Dis.* 1947 26 377 (57).

Perlstein, M. A. & H. E. Barnett: Nature and Recognition of Cerebral Palsy in Infancy *J Amer med Ass* 1952, 148 1389 (50).

Peterman, M. G Convulsions in Childhood. *Amer J Dis. Child* 1946, 72 399 (16, 50 66)

Peterman, M G Febrile Convulsions. *J Pediat* 1952, 41 537 (51).

Plum, P Cerebral Palsy *Dan. med Bull* 1956 3 99 (48 50, 56 95 101).

Polaček, L. J Vajporsky & S. Novák. EEG in Healthy Children Aged Six and Six and a Half Years. *Cesk Pediat Praha* 1965 20 946 (57).

Prechtl, H. F R.. Die Entwicklung und Eigenart frühkindlicher Bewegungsweisen. *Klin. Wschr* 1956, 34 281 (22).

Prechtl, H. F R. & J Dijkstra. *Neurological Diagnosis of Ce ebral Injury in the Newborn* In. Proc. Sympos. Prenatal Care. Noordhoff Groningen ed B. S. ten Berge 1959 (22).

Prechtl, H. F R.. The Long-term Value of the Neurological Examination of the Newborn Infant. *Little Club Clin. Develop Med* 1960 2 69 (22).

Prechtl, H. F R *Reading Difficulties as a Neurological Probl m in Childhood* In. J Money· *Reading Disability* Baltimore· The Johns Hopkins Press 1962, p. 187 (55).

Prechtl, H. F. R. & D. Beintema: The Neurological Examination of the Full Term Infant. *Little Club Clin. Develop. Med.* 1964, no. 12. (22).
Preston, M.: Late Behavioral Aspects Found in Cases of Prenatal, Natal and Postnatal Anoxia. *J. Pediat.* 1945, 26 353 (51).
Rabinovitch, R. D., A. L. Drew, R. N. De Jong, W. Ingram & L. Withey: A Research Approach to Reading Retardation. *Res. Publ. Ass. Res. nerv. ment. Dis.* 1954, 34 363. (54).
Reinhold, M.: The Effect of Laterality on Reading and Writing. *Proc. roy. Soc. Med.* 1963, 56 203. (54).
Robson, P.: Etiology of Congenital Cerebral Palsy. *Arch. Pediat.* 1962, 79 231. (49 95).
Rogers, M. & A. Lilienfeld: Prenatal and Paranatal Factors in the Development of Childhood Behavior Disorders. *Acta psychiat. scand.* 1955 suppl. 102. (51).
Rosenfeld, G. B. & C. Bradley: Childhood Behavior Sequelae of Asphyxia in Infancy. *Pediatrics* 1948, 2 74. (51).
Rossier A.: The Future of the Premature Infant. *Develop. Med. Child. Neurol.* 1962, 4 483. (102).
Roudinesco, J., G. Tardieu, M. Baron-Shewald & J. Trelat: Étude de 62 cas de lésions cérébro-méningées suivies au cours de la première enfance. *Arch. Franç. Pédiat.* 1951, 8 136. (19).
Ross, J. D., R. Strong & P. Christian: Asphyxia of the newborn infant. *Amer. J. Obstet. Gynec.* 1946, 51 : 643. (97).
Rydberg, E.: Cerebral injury in the new-born children consequent on birth-trauma. *Acta path. microbiol. scand.* 1932, suppl. 10, p. 108 and 127 (14), 140 (18) and 146 (56).
Saint-Anne Dargassies, S.: Le nouveau-né à terme: Aspect neurologique. *Biol. Neonat.* (Basel) 1962, 4 174 (22).
Schlange, H.: Elektroencephalographische Befunde bei Kindern mit Verhaltensstörungen. *Arch. Kinderheilk.* 1963, 169 123. (51).
Seitz, L.: *Ueber Hirndrucksymptome bei Neugeborenen in Folge intrakranieller Blu*tungen und mechanischer Hirninsulte. Arch. Gynäk. 1907 82 528. (12, 66).
Sidbury J. B.: The Importance of Lumbar Puncture in Intracranial Hemorrhage of the New-Born. *Arch. Pediat.* 1920, 37 545 (13).
Sitzy J. L.: *Séquelles psycho-motrices et électroencéphalographiques des hémorragies cérébro-méningées et oedèmes cérébraux des débiles et des prématurés. Strasbourg méd.* 1965 16 149 (102, 105).
Silver, A.: Behavioral Syndrome Associated with Brain Damage in Children. *Pediat. Clin. N. Amer.* 1958, 5 687 (51).
Skatvedt, M.: *Cerebral Palsy. Oslo*: Oslo University Press 1958, p. 11 (49 95), p. 15 (101).
Skydsgaard, H. B.: *Den konstitutionelle Dysleksi.* Copenhagen. Nyt Nordisk Forlag 1942. (54).
Smith, B., C. Robinson & W. G. Lennox: Acquired Epilepsy. *Neurology* 1954, 4 19 (50).
Smithells, R. W.: Prognostic Value of Neurological Examinations in the *Newborn. Cerebr. Palsy* Bull. 1961, 3 7 (22).
Steckle, G.: A Longitudinal Follow-up of Neonatal Apnea. *Child. Developm.* 1964, 35 333 (98).
Stillerman, M. L., E. L. Gibbs & M. A. Perlstein: Electroencephalographic Changes in Strabismus. *Amer. J. Ophthal.* 1952, 35 54. (57).
Sundal, A.: Die Prognose der Frühgeborene und die Prophylaxe des Geburtstraumas. *Acta obstet. gynec. scand.* 1930, 9 475 (101 102).
Thom, D. A.: Convulsions of early life and *their relation* to the chronic convulsive disorders and mental defects. *Amer. J. Psychiat.* 1942, 98 574. (49).
Thomson, C.: Some considerations regarding the aetiology, the incidence and the course of concomitant *strabismus. Trans. ophthal. Soc. U. K.* 1924, 44 238. (56).

McPhail, F L. & E. L. Hall. Consideration of Cause and Possible Late Effect of Anoxia in the Newborn Infant. *Amer J Obstet Gynec* 1941 42 686 (97).

Millar J H D Epilepsy and Strabismus. *Epilepsia* 1965 6 43 (56).

Munro, D & R. S. Eustis. The Diagnosis and Treatment of Intercranial Hemorrhage in the Newborn. *Am J Dis Child* 1922, 24 273 (13).

Munro, D., Cranial and Intracranial Damage in the Newborn. *Surg Gynec Obstet*, 1928 47 622. (17).

Munro, D Symptomatology and Immediate Treatment of Cranial and Intracranial Injury in the Newborn, Including Intracranial Hemorrhage. *New Engl J Med* 1930 203 502. (17).

Mörstad O & B R. Kaada. Electroencephalographic Studies of Infants and Children who Acquired Intracranial Injuries at Birth. *Neurology (Minneap)* 1953 3 544 (57)

Naujoks, H.. Das spätere Schicksal der Kinder mit intrakraniellen Geburtsläsionen. *Mschr Geburtsh Gynäk* 1928, 80 297 (17).

Nicholls, J V V.. Congenital Dyslexia. A Problem in Etiology *Canad med. Ass. J* 1960 82 575 (54)

Nicholls, J V V Reading Difficulties in Children. *Int Ophthal Clin.* 1965 5 423 (54).

Nielsen, H H.. *A Psychological Study of Cerebral Palsied Children.* Copenhagen. Munksgaard 1966. (51).

Nielsen, J M & C. B. Courville: Role of Birth Injury and Asphyxia in Idiopatic Epilepsy *Neurology* 1951 1 48 (50).

Orton, S. T.. *Arch Neurol Psychiat* 1925 14 581 (54).

Orton, S. T.. *Reading Writing and Speech Problems in Children.* London. Chapman & Hall 1937 p. 200 (54).

Pache, H D Die Klinik der kindlichen Krampfleiden. *Mschr Kinderheilk* 1954 102 42. (49).

Paine, R S.. The Immediate Value of the Neonatal Neurological Examination. *Little Club Clin. Develop. Med* 1960, 2 62. (22).

Pasamanick, B. & A. M Lilienfeld Association of Maternal and Fetal Factors with Development of Mental Deficiency *J Amer med. Ass* 1955 159 155 (49).

Pasamanick, B. & A. M. Lilienfeld. Maternal and Fetal Factors in the Development of Epilepsy *Neurology* 1955 5 77 (50).

Peiffer J Morphologische Aspekte der Epilepsien. *Monogr gesamt Neurol Psychiat* 1963 100 p. 127 (51).

Perlstein, M.A., E. L. Gibbs & F A. Gibbs: The electroencephalogram in infantile cerebral palsy *Res. Publ. Ass nerv ment Dis.* 1947 26 377 (57).

Perlstein, M. A. & H E. Barnett: Nature and Recognition of Cerebral Palsy in Infancy *J Amer med Ass.* 1952, 148 1389 (50).

Peterman, M. G Convulsions in Childhood. *Amer J Dis Child* 1946, 72 399 (16, 50, 66).

Peterman, M G Febrile Convulsions. *J Pediat* 1952, 41 537 (51).

Plum, P Cerebral Palsy *Dan. med Bull.* 1956, 3 99 (48, 50, 56, 95 101).

Poláček, L. J Vajporský & S. Novák· EEG in Healthy Children Aged Six and Six and a Half Years. *Česk. Pediat Praha* 1965 20 946. (57).

Prechtl, H F R. Die Entwicklung und Eigenart frühkindlicher Bewegungsweisen. *Klin. Wschr* 1956, 34 281 (22).

Prechtl, H F R. & J Dijkstra. *Neurological Diagnosis of Cereb al Injury in the New born.* In. Proc. Sympos. Prenatal Care. Noordhoff Groningen ed. B. S. ten Berge 1959 (22).

Prechtl, H. F R. The Long-term Value of the Neurological Examination of the New born Infant. *Little Club Clin. Develop Med* 1960, 2 69 (22).

Prechtl, H. F R. *Reading Difficulties as a Neurological Problem in Childhood.* In. J Money· *Reading Disability* Baltimore: The Johns Hopkins Press 1962, p. 187 (55).

Subject Index

Trojaborg, W. Focal Spike Discharges in Children, a Longitudinal Study *Acta paediat. (Uppsala)* 1966, suppl. 168 p. 41 (57).

Usdin, G L. & M. L. Weil. Effect of Apnea Neonatorum on Intellectual Development. *Pediatrics*. 1952, 9 387 (97).

Ucko, L. E. A Comparative Study of Asphyxiated and Non-Asphyxiated Boys from Birth to Five Years. *Develop Med Child. Neurol* 1965 7 643 (97).

Walker W L. Premature Children with Birth Asphyxia. *Develop Med. Child Neurol.* 1964 6 458 (98).

Wetterdal, P. Senprognos för asphyktiska tångförlösta barn. *Nord Med.* 1951 45 1000 (96).

Wohlmuth, G & R. Frater Late Sequelae of Prematurity *Acta paediat. Acad Sci. hung* 1965 6 297 (101 102, 105).

Ylppö, A. Zur Physiologie, Klinik und zum Schicksal der Frühgeborenen. *Zschr Kinderheilk* 1919 24 1 (101 102, 105).

Zangwill, O L. *Cerebral Dominance and its Relation to Psychological Function.* Edinburgh. Oliver & Boyd 1960 p. 25 (55).

Znamenacek, K., J Horsky V Jirsova & V Melichar A Clinical Study of Perinatal Trauma in Newborn Infants. *Étud néonatal* 1957 6 79 (20, 66).

Subject Index

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 194 1969

STUDIES ON THE SERUM BINDING OF *VITAMIN* B_{12} IN THE NEWBORN HUMAN INFANT

BY ANTTI KUMENTO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

STUDIES ON THE SERUM BINDING OF VITAMIN B_{12} IN THE NEWBORN HUMAN INFANT

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 194, 1969

From The Hematology and Radioisotope Research Laboratories
Veterans Administration Hospital, Albany New York

STUDIES ON THE SERUM BINDING OF VITAMIN B_{12} IN THE NEWBORN HUMAN INFANT

by

Antti Kumento

Present address: Children's Hospital of Turku University
Turku Finland

ACTA PAEDIATRICA SCANDINAVICA
SUPPLEMENT 194, 1969

From The Hematology and Radioisotope Research Laboratories Veterans Administration Hospital Albany New York

STUDIES ON THE SERUM BINDING OF VITAMIN B_{12} IN THE NEWBORN HUMAN INFANT

by

Antti Kumento

Present address Children's Hospital of Turku University Turku Finland

TURKU 1969

Preface

This study was carried out in the Hematology and Radioisotope Research Laboratories of the Veterans Administration Hospital, Albany New York, during my research fellowship in the Department of Pediatrics, Albany Medical College of Union University Albany New York, from September 1966 through August 1967 My chief Dr Charles A. Hall, M D Professor of Medicine in Albany Medical College suggested me this study and made the performance of it possible. His wide knowledge and experience in the field of vitamin B_{12} research, as well as his stimulating encouragement were of primary importance to me throughout this work.

The chief biochemist of our laboratory Mr Alexander E. Finkler B.S., deserves my sincere thanks for his ever available assistance His thorough knowledge and technical skills in the field of vitamin B_{12} binders were essential for the performance of this study

Dr A Leonard Luhby M D Professor of Pediatrics in New York Medical College and Chief Section of Hematology was one of the initiators of the present study I am very grateful for the many stimulating discussions I had with him and with Dr Jack M. Cooperman, Ph.D The group of Dr Luhby provided the infant blood samples for this study

Miss Mary E. Rappazzo, M.S. deserves my most sincere thanks for nice and competent assistance. Mr Edward S Allen performed the vitamin B_{12} assays. The drawings for this publication were made by the Medical Illustration Service of the Veterans Administration Hospital and partly by the Medical Illustration Service of Albany Medical College. Dr Hall and Miss Rappazzo revised the language of my text.

The preparation of the manuscript was completed at the Children's Hospital of Turku University Finland. My thanks are due to my present chief, Professor Tuomas Peltonen, M.D who has given all his support to me during this work. I am grateful to Docent Ruth Wegelius, M D for valuable discussions. Secretarial assistance was provided by Miss Irja Montonen.

This work was supported in part by Grant AM02608 of the U.S Public Health Service.

Turku, January 1969

Antti Kumento

Preface

This study was carried out in the Hematology and Radioisotope Research Laboratories of the Veterans Administration Hospital, Albany, New York, during my research fellowship in the Department of Pediatrics, Albany Medical College of Union University, Albany, New York, from September 1966 through August 1967. My chief, Dr. Charles A. Hall, M.D., Professor of Medicine in Albany Medical College, suggested me this study and made the performance of it possible. His whole knowledge and experience in the field of vitamin B_{12} research, as well as his stimulating encouragement were of primary importance to me throughout this work.

The chief biochemist of our laboratory, Mr. Alexander E. Finkler, B.S., deserves my sincere thanks for his ever available assistance. His thorough knowledge and technical skills in the field of vitamin B_{12} binders were essential for the performance of this study.

Dr. A. Leonard Lubby, M.D., Professor of Pediatrics in New York Medical College and Chief, Section of Hematology, was one of the initiators of the present study. I am very grateful for the many stimulating discussions I had with him and with Dr. Jack M. Cooperman, Ph.D. The group of Dr. Lubby provided the infant blood samples for this study.

Miss Mary E. Rapparzo, M.S. deserves my most sincere thanks for nice and competent assistance. Mr. Edward S. Allen performed the vitamin B assays. The drawings for this publication were made by the Medical Illustration Service of the Veterans Administration Hospital and partly by the Medical Illustration Service of Albany Medical College. Dr. Hall and Miss Rapparzo revised the language of my text.

The preparation of the manuscript was completed at the Children's Hospital of Turku University, Finland. My thanks are due to my present chief, Professor Tuomas Peltonen, M.D., who has given all his support to me during this work. I am grateful to Docent Ruth Wegelius, M.D. for valuable discussions.

Secretarial assistance was provided by Miss Irja Montonen.

This work was supported in part by Grant AM02808 of the U.S. Public Health Service.

Turku, January 1969

Antti Kumento

CONTENTS

Abbreviations

B_{12}	vitamin B_{12}
IF	intrinsic factor
TC I	transcobalamin I
TC II	transcobalamin II
FTC	fetal transcobalamin
DEAE	diethylaminoethyl cellulose
CM	carboxymethyl cellulose

Abbreviations

B_{12}	vitamin B_{12}
IF	intrinsic factor
TC I	transcobalamin I
TC II	transcobalamin II
FTC	fetal transcobalamin
DEAE	diethylaminoethyl cellulose
CM	carboxymethyl cellulose

Introduction

Several peculiarities in the metabolism of vitamin B_{12} in the fetus and the newborn have been established by previous investigations

— There is a *significant difference* between maternal and fetal serum vitamin B_{12} levels in favor of the fetus.

— There is an active transport process for vitamin B_{12} across the placenta.

— The tissue vitamin B_{12} concentrations in the fetus differ from the adult concentrations.

— The initially high serum vitamin B_{12} concentration changes rapidly during the early weeks of life

— There is an intrinsic factor independent system for intestinal uptake of vitamin B_{12} in the newborn rat.

The above listed features will be reviewed in detail in the following section.

The present study was undertaken to investigate whether any abnormalities in serum vitamin B_{12} binding were connected to the peculiarities listed above. The principle was to label serum proteins with Co-vitamin B_{12} *in vitro* and to fractionate the labeled serum by various methods in order to separate and characterize the vitamin B_{12} binders.

Part of the results were presented in a preliminary form before the National Meeting of the American Federation for Clinical Research in April 1967 (Kumento *et al.* 1967)

Introduction

Several peculiarities in the metabolism of vitamin B_{12} in the fetus and the newborn have been established by previous investigations:

— There is a significant difference between maternal and fetal serum vitamin B_{12} levels in favor of the fetus.

— There is an active transport process for vitamin B_{12} across the placenta.

— The tissue vitamin B_{12} concentrations in the fetus differ from the adult concentrations.

— The initially high serum vitamin B_{12} concentration changes rapidly during the early weeks of life.

— There is an intrinsic factor independent system for intestinal uptake of vitamin B_{12} in the newborn rat.

The above listed features will be reviewed in detail in the following section.

The present study was undertaken to investigate whether any abnormalities in serum vitamin B_{12} binding were connected to the peculiarities listed above. The principle was to label serum proteins with Co-vitamin B_{12} *in vitro* and to fractionate the labeled serum by various methods in order to separate and characterize the vitamin B_{12} binders.

Part of the results were presented in a preliminary form before the National Meeting of the American Federation for Clinical Research in April 1967 (Kumento *et al.* 1967).

Review of Literature

The following aspects of the metabolism of vitamin B_{12} during pregnancy and the neonatal period have been studied

— serum vitamin B_{12} levels during pregnancy

— the relationship between maternal and fetal serum B_{12} concentrations at the time of delivery

— the transplacental passage of vitamin B_{12} in rat guinea pig dog and man

— tissue concentrations of vitamin B_{12} in the human fetus

— serum vitamin B_{12} concentrations during early infancy

— the peculiarities in the intestinal absorption of vitamin B_{12} in the newborn

The results of these studies will be reviewed Additionally a brief review will be presented about the serum binding of vitamin B_{12}

Concentration of vitamin B_{12} in the serum of pregnant women

The first report about the serum B_{12} concentrations during pregnancy is by Heinrich (1954) He studied the sera of 185 pregnant and puerperal women Twenty percent of them had a lower than normal level of serum B_{12} and simultaneously low urinary excretion of B_{12} He attributed these phenomena to the increased need of B_{12} caused by pregnancy The work of Heinrich has been followed by a large number of investigations confirming the low levels of serum B_{12} during pregnancy Boger *et al* (1956 1957a) demonstrated low serum B_{12} levels in their study of 509 pregnant women They also demonstrated a direct and statistically significant correlation between serum level of vitamin B_{12} and duration of pregnancy Other studies showing the decreased serum B_{12} levels are e g those by Karlin (1955) Baker *et al* (1957) Young *et al* (1959) Hansen (1959) Lavrinne *et al* (1960) Lowenstein *et al* (1960) and Ball and Giles (1964) Lowenstein *et al* also presented evidence for other factors besides hemodilution being responsible for the lowering of serum B_{12} levels during pregnancy Hellegers *et al* (1957) and Chow *et al* (1958) showed that pregnancy increases the intestinal absorption of vitamin B_{12} both in man and in rat and thus supported the concept that an increased demand rather than a limited supply of vitamin B_{12} is responsible for the observed low serum B_{12} levels. Lubby *et al* (1961a) however found a decreased intestinal absorption of vitamin B_{12} during the last few weeks of pregnancy in man Young *et al* (1959) showed that rapid successive pregnancies cause a marked depression of maternal serum B_{12} levels. Ball and Giles (1964) did not confirm this on their material

Somewhat different results were obtained by Gotchel and Lovett (1960) They found declining serum B_{12} concentrations during pregnancy with a sharp rise 4—6 weeks *ante partum* Lawrence and Klipstein (1967) found low serum B_{12} values in a group of anemic and non-anemic pregnant women They retested 11 sera by the coated charcoal assay based on isotope dilution and found normal values in nine of the retested sera. The authors suggested that serum B_{12} values in pregnant women may in fact be normal and the low values obtained by microbiological assays may be caused by some inhibitory agent The eleven above cases are the only reported pregnant women tested by other

than microbiological methods, and obviously more work is needed to clarify this aspect. Sullivan et al. (1967) were not able to demonstrate any decrease in the serum B_1 concentration during pregnancy using a microbiological assay.

The capacity of serum to bind added B_1 has been reported to be increased during pregnancy (Pratowsky et al. 1959, Sadovsky et l. 1959, Lowenstein et al. 1960, Sullivan t al. 1967).

The difference in serum concentration of vitamin B_1 between mother and fetus

Killander and Vahlqvist (1954) were the first ones to report the difference in serum B concentration between mother and f tus. This transplacental concentration gradient in favor of the f tus has been confirmed by a large number of investigations, e.g. Karlin and Dumont (1955), Okuda et al. (1956), Boger et l. (1957a, 1957b), Dumont and Karl n (1957), Dixit et al. (1957), Killander 1957), Baker et al. (1958), Prystowsky et al. 1959), Sadovsky et l. (1959), Lowenstein t al. (1960), Luhby et al. (1961a, 1961b) and Zachau-Christiansen et al. (1962). In the serum f Zachau-Christiansen et al. the aver age maternal serum B_1 concentration was 40 pg ml and cord serum B_{12} concentration 3 0 pg ml, whereas Luhby et l. (1961b) reported values f 177 pg ml and 931 pg/ml f r mat rnal and cord serum, respectively. Both groups used a modification of the *Lactobacillus lactis* assay.

There is one situation where fetal B_{12} level as judged by cord serum, has been reported t be ex ptionall low. Okuda et al. (1956), *Hellegers t al.* (1957) and Chow and Okuda 1960) gave reports on four cases of con genital tetina who ll had very low levels f serum itamin B_1 at birth. They had no knowledge f congenital eretina with normal serum B concentrations at birth.

The transplacental passage of vitamin B_{12}

The studies referred to in the previous chapter already indirectly show that there is an active transport of B_{12} across the placenta producing the transplacental concentration gradient of vitamin B_{12} in favor of the fetus. There is also direct experimental evidence for such a phenomenon.

Chow et al. (1951) injected relatively large amounts of radioactive vitamin B_{12} into pregnant rats and measured the radioactivity in the ffsprings. They detected a total of 18 % of the injected dose in the fetuses an l the placentas, whereas amniotic fluid was free from radioactivity. Karlin (1956, 1957) studied the distribution of vitamin B after oral and parenteral administration to preg nant guinea pigs. She found an accumulation of vitamin B_1 in both maternal and fetal tissues and in the placenta. Hellegers et al (1957) performed elegant studies feeding or injecting small doses of radioactive vitamin B_1 to pregnant rats. They observed that about 60 % of the radioactivity passed to the f tuses and much less radioactivity accumu lated in the maternal organs when compared t nonpregnant rats treated similarly. Rice et al. (1958) obtained the same kind of results using huge doses of radioactive vita min B_{12}.

Luhby et al. (1958, 1959a, 1961a) studied the placental transfer of vitamin B_{12} in man using tracer amounts of Co-labeled B . Their results showed that B_{12} administered at the end of pregnancy first built up in the placenta for the first two days and then gradually passed to the fetal side over a —3 week period, to a maximum transfer of 33—45 % of the administered dose. 1— % f the dose remained in the placental tissue. They were also able to show that only newly administered B_{12} was available for placental transfer. Radioactive B_{12} which was present in the maternal liver from the time before

Review of Literature

The following aspects of the metabolism of vitamin B_{12} during pregnancy and the neonatal period have been studied
— serum vitamin B_{12} levels during pregnancy
— the relationship between maternal and fetal serum B_{12} concentrations at the time of delivery
— the transplacental passage of vitamin B_{12} in rat guinea pig dog and man
— tissue concentrations of vitamin B_{12} in the human fetus
— serum vitamin B_{12} concentrations during early infancy
— the peculiarities in the intestinal absorption of vitamin B_{12} in the newborn

The results of these studies will be reviewed. Additionally a brief review will be presented about the serum binding of vitamin B_{12}.

Concentration of vitamin B_{12} in the serum of pregnant women

The first report about the serum B_{12} concentrations during pregnancy is by Heinrich (1954). He studied the sera of 185 pregnant and puerperal women. Twenty percent of them had a lower than normal level of serum B_{12} and simultaneously low urinary excretion of B_{12}. He attributed these phenomena to the increased need of B_{12} caused by pregnancy. The work of Heinrich has been followed by a large number of investigations confirming the low levels of serum B_{12} during pregnancy. Boger *et al* (1956, 1957a) demonstrated low serum B_{12} levels in their study of 502 pregnant women. They also demonstrated a direct and statistically significant correlation between serum level of vitamin B_{12} and duration of pregnancy. Other studies showing the decreased serum B_{12} levels are e.g. those by Karlin (1955), Baker *et al* (1957), Young *et al* (1959), Hansen (1959), Layrisse *et al* (1960), Lowenstein *et al* (1960) and Ball and Giles (1964). Lowenstein *et al* also presented evidence for other factors besides hemodilution being responsible for the lowering of serum B_{12} levels during pregnancy. Hellegers *et al* (1957) and Chow *et al* (1958) showed that pregnancy increases the intestinal absorption of vitamin B_{12} both in man and in rat and thus supported the concept that an increased demand rather than a limited supply of vitamin B_{12} is responsible for the observed low serum B_{12} levels. Lubby *et al* (1961a) however found a decreased intestinal absorption of vitamin B_{12} during the last few weeks of pregnancy in man. Young *et al* (1959) showed that rapid successive pregnancies cause a marked depression of maternal serum B_{12} levels. Ball and Giles (1964) did not confirm this on their material.

Somewhat different results were obtained by Gotchel and Lovett (1960). They found declining serum B_{12} concentrations during pregnancy with a sharp rise 4—6 weeks *ante partum*. Lawrence and Klipstein (1967) found low serum B_{12} values in a group of anemic and non-anemic pregnant women. They retested 11 sera by the coated charcoal assay based on isotope dilution and found normal values in nine of the retested sera. The authors suggested that serum B_{12} values in pregnant women may in fact be normal and the low values obtained by microbiological assays may be caused by some inhibitory agent. The eleven above cases are the only reported pregnant women tested by other

compared to fetuses at a similar stage of development. It is thus possible that a severe enough maternal B_{12} deprivation leads to fetal death.

Satoskar et al. (1961) dealt with an other type of disturbed maternal B_{12} metabolism. In their material the mothers had exceptionally high serum B_{12} levels due to malnutritional liver disease. Even then, the cord serum B levels were generally higher than the mat rnal levels.

Fetal tissue concentrations of vitamin B_{12}

The vitamin B_{12} concentrations in human fetal tissues have been studied by Killander (1958) and extensively by Salmi (1963). The concentrations w re found to be at the same levels during the studied period of intrauterine life with the exception of the central nervous tissue where a declining trend was noticed with advancing maturity. According to Salmi, the highest concentration was represented by the kidney the adrenal gland, and the liver f llowed by the thyroid gland. He noticed further that the tissue B levels in the same fetus w re throughout high or low and attributed this t the maternal supply of vitamin B t the f tus.

Neither Killande nor Salmi published adult tissue B_{12} levels for comparison. There re man studies by different investigators f the adult B tissue concentrations, human live especially has been extensively studied. Good review concerning adult tissue B concentrations were presented e.g. by Salmi 1963) nd by Ståhlberg et al. (1967). Direct comparisons between the results from dif f rent laboratories are not reliable especially hen dealing with such a complicated test as the det rmination of tissue B_{12} concentration. Howev if one compares the results f Salmi to the unpublished results of Hall 1967) it seems obvious that the fetal liver has lower B_{12} concentration than the adult liver whereas other fetal concentrations are either higher or the same as adult concentrations.

To overcome the difficulties in comparing results from different laboratories, Rappazzo et al. (1968) undertook a study on this subject. Their results showed that the B_{12} concentration in fetal liver is lower than that in adult liver. Various levels of significant differences were also found in comparing fetal and adult kidney spleen, heart, lung, brain and colon. The B concentration in fetal thyroid was higher than the adult concentration, this difference was significant at the 5 % level. The other tissue B concentrations w re at about the same levels in adults and fetuses.

As to the liver it is not surprising to find a low B_{12} concentration in the fetus. The liver is functionally immature at birth (reviewed e.g. by Schellong 1962) and its gross circulation, as well as the circulation at the arteriole level is different from the adult circulation (Järvikka 1964). Thus the low B_{12} concentration probably reflects the state of the liver more than the peculiarities in the metabolism of vitamin B_{12}.

On the other hand, the thyroid gland is known to be metabolically active at birth. This was confirmed e.g. by Peltonen and Hirvonen (1964, 1965) who discovered the rapid recovery of high infant protein-bound iodine values after the transitory lowering by exchange transfusions. Another interesting correlation is that reported by Chow and Okuda (1960) namely the low serum B_{12} values in congenital cretins. This correlation was discussed e.g. by Salmi (1963). The relationship between these two co-existent phenomena is unexplained so far

The serum B_{12} concentrations during early infancy

Luhby et al (1961b) followed the serum concentrations of vitamin B during early

conception was not at all transferred to the fetus.

Luhby *et al* (1959b) and Woods *et al* (1960) studied the transplacental passage of vitamin B_{12} in dog and confirmed the transfer of B_{12} from the maternal circulation to the fetus through the placenta. Danesino and Montemagno (1961) studied the same situation in guinea pigs. Their observation period was only 15 minutes after an intravenous injection of B_{12} during which short time the administered B_{12} started to accumulate in the placenta but did not pass to the fetal side

Salmi (1963) studied the fetal distribution of labeled B_{12} injected into pregnant rats. He found the maximum concentrations of labeled B_{12} in fetal kidney liver adrenal and thyroid gland. The distribution of nonradioactive B_{12} was found to be the same as to the order of concentration

There is thus ample evidence about the placental transfer of vitamin B_{12}, and even the mode of transmission has been clarified to some extent in the investigations cited above. Analogous situations of the transplacental concentration gradient of vitamin B_{12} exist even for some other vitamins and iron Chow and Okuda (1960) studied fetal and maternal serum concentrations of vitamin C vitamin B_6, and iron all of which were in higher concentrations in the fetus. The transplacental concentration gradient of serum folic acid in favor of the fetus was demonstrated *e g* by Baker *et al* (1958) Zachau Christiansen *et al* (1962) and Giles (1966) Zachau-Christiansen *et al* also confirmed the concentration gradient for serum iron Wöhler (1964) studied the metabolic phenomena in the transport of iron through the placenta Räihä (1958) published an extensive experimental study on the placental transfer of vitamin C Lust *et al* (1954) presented a detailed model for the transplacental passage of riboflavin against a concentration gradient It is thus obvious that the transplacental concentration gradient and active placental transport of vitamin B_{12} are not unique They rather reflect a common feature in the placental function

The effect of maternal B_{12} deficiency on the fetus

There are several animal studies concerning the untoward effects of severe maternal B_{12} deficiency on the fetus (*e g* Lepkovsky *et al* 1951 Jones *et al* 1955) Nesbitt and Chow (1958) presented a general review of the earlier studies. Woodard and Newberne (1967) reviewed the literature and reported a detailed study concerning the pathogenesis of hydrocephalus in the offsprings of B_{12} deficient rats.

Salmi (1963) studied the phenomenon in a more physiologic manner producing only marginal B_{12} deficiency in rats. A low vitamin B_{12} diet for the dam distinctly lowered the fetal tissue concentrations of B_{12}. The lowering was most manifest in the brain tissue and a sharp decline was noticed in the kidney whereas the decrease in concentration was least in the liver

The information concerning the effects of B_{12} deficiency on developing human fetus is scanty Baker *et al* (1962) studied nine untreated B_{12} deficient delivering mothers and their infants in India. All the mothers were frankly B_{12} deficient by several criteria Seven of them gave birth to healthy full term infants. Interestingly the cord serum B_{12} levels of these infants were markedly higher than the maternal serum B_{12} levels, although lower than reported for cord serum by other investigators. Only one of the seven infants had intermediate megaloblasts in the bone marrow Thus, the fetus seems to be able to get its share of vitamin B_{12} even when the mother is in a state of deficiency Two of the mothers delivered stillborn premature fetuses. Their liver content of vitamin B_{12} was analyzed and found to be distinctly lower as

suggested different functions in the process f B_{12} transport for the different binding sites. Later on they were able to clearly separate the "early stage binder" from the previously known -globulin B_{12} binder (*Hall* and Finkler 1963). In a study on the dynamics of the B binders (*Hall and Finkler* 1965) the current nomenclature for the binders was introduced and their properties and functions were described and discussed. The trace plasma protein which bound vitamin B_{12} after parenteral or oral intake was isolated and designated transcobalamin II TC II). Its behavior on *DEAE*- and CM cellulose chromatographies was studied, and t was shown to have β-globulin mobility in lectrophoresis. Labeled B_{12} bound to TC II disappeared rapidly from the circulation. It was concluded that the *function of TC II is* transport system for the phase of B_{12} metabolism immediately after intake. The other B binder the carrier f endogenous B_{12}, was found t bind little of the added B It was designated TC I. The B bound to it had a much slower turnover.

Subsequently Hall and Finkler (1966a) studied the serum binding of *in vitro* added B The binding corresponded t the pattern found immediately aft r a vivo administration f the vitamin with main binding to TC II and little binding to TC I. When large amou ts of B w re added, other proteins besides TC II and TC I participated in the binding. These were considered to be secondary r nonspecific binders.

Cooper and Paranchych (1961) showed that mouse ascites fluid and human serum produced a twenty fold increase of uptake of vitamin B by mouse ascites tumor cells and H La cells. Finkler and Hall (1967) studied the same phenomenon using isolated B binders. Analogous to their arlier vitro observat ons, TC II was found to promote the uptake f B by human normal and malignant cells, whereas neither TC I nor the othe studied binders (from erythrocytes, leukocytes, saliva, and gastric juice) enhanced the uptake of B_{12} by the cells *in vitro*. Additionally evidence was obtained for TC I being an exit carrier for cell vitamin B_{12}.

Retief *et al.* (1967a) described two serum B_{12} binders which they called α-binder and *β-binder*. The former corresponds to TC I and the latter to TC II. Their group also studied the relation of the binders to the uptake of vitamin B_{12} by reticulocyte-rich erythrocytes (Retief *et al.* 1967b). They found the β-binder to deliver more B_{12} to erythrocytes than the α-binder.

An important contribution to the present knowledge about serum B_{12} binders comes from Hom and his co-workers. Hom *et al.* (1966) fractionated *in vitro* labeled serum by various methods and confirmed the earlier results of *Hall* and Finkler. The molecular weights for serum B_{12} binders were determined by Hom and Olesen (1967) using Sephadex gel filtration. A mean value of 1.3 000 was obtained for TC I and 38,000 for TC II. Hom (1967a) gave important information concerning the behavior of TC II *in vitro*. He demonstrated that TC II complexes and binds to Sephadex at low ionic strength. The resulting TC II complex has a molecular weight f over 200 000. A well designed study on the plasma turnover of $^{57}CoB_{12}$ bound to TC I and TC II was published by Hom (1967b). He showed that the labeled transcobalamins were diluted into a volume which was 2—3.1 times larger than the plasma volume. The half life of TC II $^{57}CoB_{12}$ complex was 1.5 hours and that of TC I CoB complex 9.3 days. When $^{57}CoB_{12}$-TC II was injected intravenously the label appeared bound to TC I in four hours after the injection, and was completely in that form 24 hours after the injection. The removal of TC II CoB$_{12}$ reported by Hom is slower than that given by Finkler and Hall (1967) this can be explained by the use of different points of time for analyzing the disappearance curve.

infancy. Their mean value for the cord serum B_{12} concentration was 951 pg/ml, the value remained high for the first week and then rapidly decreased to an average of 312 pg/ml by one month. Further gradual decline to 228 pg/ml occurred by 6—7 months, followed by a slow rise to 403 pg/ml by 24—36 months of age. The results reported by Bar-Shany and Herbert (1967) are in agreement with those of Luhby *et al.* cited above.

The intestinal absorption of vitamin B_{12} in the newborn

Boass and Wilson (1964) studied the mechanism of intestinal uptake of vitamin B_{12} in newborn rats. The intestine from fetal and newborn rats showed extremely high uptake of the vitamin in the absence of intrinsic factor (IF). The stomach wall of fetal and newborn rats contained less than 1 % of the IF found in the adult rat. After the first week of life the amount of IF increased rapidly and simultaneously the IF independent uptake system decreased in activity. Newborn guinea pigs showed little uptake of B_{12} in the absence of IF. The authors suggested that the phenomenon in newborn rats may be connected with their ability to absorb large protein molecules by pinocytosis. The timing of the phenomena is the same and neither of them is found in the guinea pig. An interesting discussion concerning this subject is presented in connection with an article by Wilson (1966).

Salmi (1966) studied the absorption of labeled B_{12} from the digestive canal of guinea pig fetuses and newborn animals. He did not find any increase in the absorptive capacity during the development.

Little is known about the intestinal absorption mechanism of B_{12} in the newborn human infant. Luhby *et al.* (1958) fed tracer doses of $^{60}CoB_{12}$ to newborn infants and reported an absorption of 75—95 % whereas pregnant women absorbed only 27—70 %. Agunod *et al.* (1967) from the same laboratory studied the intrinsic factor secretion in newborn infants and found little biological IF-activity during the first week of life. According to these two studies, an IF independent mechanism for B_{12} absorption cannot be excluded. There are however divergent views on the presence of IF in newborn human infants. Bar-Shany and Herbert (1967) and Goldberg *et al.* (1967) using different methods than Agunod *et al.* concluded that intrinsic factor is present in the gastric juice of newborn infants.

The binding of vitamin B_{12} by serum proteins

Pitney *et al.* (1954) found the vitamin B_{12} in serum to be mainly bound with proteins in the α-globulin electrophoretic fraction. This finding has since been confirmed by several investigators, e.g. Mendelsohn *et al.* (1958), Weinstein *et al.* (1959), Banerjee *et al.* (1963) and Hardwicke and Jones (1966). A detailed review of the earlier studies was presented by Simons (1964). The B_{12} binding protein in serum was shown to be an α-globulin and a constituent of the seromucoid fraction.

Miller (1958) presented experiments showing the different mode of serum binding for *in vitro* added B_{12} when compared to native or endogenous B_{12}. He found the added B_{12} bound mainly with a β globulin. This difference has since been confirmed by various methods (Miller and Sullivan 1959a, 1959b, Simons 1964, Gabuzda *et al.* 1965).

This duality in the binding of vitamin B_{12} by serum proteins was clarified by the works of Hall and Finkler. In a study using intravenous administration of labeled B_{12} they showed the binding of B_{12} in more than one plasma fraction (Hall and Finkler 1962). The rate of B_{12} disappearance from each fraction was different so that the plasma binding pattern changed with time. This

suggested different functions in the process of B_{12} transport for the different binding cit a. Later on they were able to clearly separate the early stage binder" from the previously known -globulin B_{12} binder (Hall and Finkler 1963). In a study on the dynamics of the B binders (Hall and Finkler 196.) the current nomenclature for the binders was introduced and their properties and functions w re described and discussed. The trace plasma protein which bound vitamin B_{12} after parenteral or oral intake, was isolated and designated transcobalamin II (TC II). Its behavior on DEAE- and CM cellulose hromatographies was studied, and it was shown to have β-globulin mobility in electrophoresis. Labeled B_1 bound to TC II isappeared rapidly from the circulation. It was concluded that the function of TC II is transport syst m for the phase of B_{12} metabolism immediately after intake. The other B binder the carrier f endogenous B_{12}, was found t bind little of the added B_{12}. It was designated TC I. The B bound to it ha l a much slower turnover.

Subsequently Hall and Finkler (1966a) studied the serum binding of n vitro added B. The binding corresponded to the pattern f und immediat l aft r i vivo administration f the vitamin, with main binding to TC II and little binding t TC I. When large amount f B_1 w re added, other proteins besides TC II and TC I participated in the bind ng. These w re considered t be secon lary or nonspecific binders.

Cooper and Laranchych (1961) showed that mouse asc tes fluid and human serum produced twenty fold ncrease f uptake of vitamin B by mouse ascites tumor cells and h H La cells. Finkle and Hall (1967) studied the same phenomenon using isolated B binders. Analogous to their earlier in vitro observations, TC II was found t promote the uptake f B by human normal and malignant cells, wh reas neither TC I nor the other studied binders (from erythrocytes, leukocytes, saliva, and gastric juice) enhanced the uptake of B_{12} by the cells in vitro. Additionally evidence was obtained for TC I being an exit carrier for cell vitamin B_{12}.

Retief et al. (1967a) described two serum B_1 binders which they called α-binder and β-binder. The former corresponds to TC I and the latter to TC II. Their group also studied the relation of the binders to the uptake of vitamin B_{12} by reticulocyte-rich erythrocytes (Retief et al. 1967b). They found the β-binder to deliver more B_{12} to erythrocytes than the α-binder.

An important contribution to the present knowledge about serum B_{12} binders comes from Hom and his co-workers. Hom et al (1966) fractionated in vivo labeled serum by various methods and confirmed the earlier results of Hall and Finkler. The molecular weights for serum B_{12} binders were determined by Hom and Olesen (1967) using Sephadex gel filtration. A mean value of 1 1,000 was obtained for TC I and 38,000 for TC II. Hom (1967a) gave important information concerning the behavior of TC II in vitro. He demonstrated that TC II complexes and binds to Sephadex at low ionic strength. The resulting TC II complex has a molecular weight of over ?00,000. A well designed study on the plasma turnover of CoB_{12} bound to TC I and TC II was published by Hom (1967b). He showed that the labeled transcobalamins were diluted into a volume which was ?—3.1 times larger than the plasma olume. The half life of TC II $^{57}CoB_{12}$ complex was 1.5 hours and that of TC I $^{57}CoB_{12}$ complex 9.3 days. When $^{57}CoB_{12}$-TC II was injected intravenously the label appeared bound to TC I in four hours after the injection, and was completely in that form ?4 hours after the injection. The removal of TC II $^{57}CoB_{12}$ reported by Hom is slower than that given by Finkler and Hall (1967); this can be explained by the use of different points of time for analyzing the disappearance curve.

The vitamin B_{12} binding capacities of serum transcobalamins were studied by Hom and Ahluwalia (1968), using *in vitro* labeling and Sephadex G 200 gel filtration for the separation of the binders. TC I bound up to 47.1 % of the added B_{12}, with a range from 8.5 to 47.1 % or from 72 to 1057 pg/ml, in different individual sera. TC II bound from 650 to 1891 pg/ml accounting for up to 90.3 % of the unsaturated binding capacity. The authors also abruptly introduced a third, large-sized binder termed TC 0. It was found to bind from 0 to 70 pg/ml accounting for up to 5.2 % of the serum unsaturated B_{12} binding capacity. TC 0, I and II were the only binders of added B_{12} over the studied range from 75 to 20 760 pg/ml. There was an excess of B_{12} when large amounts were added and this excess remained unbound. The relative amounts of B_{12} bound to TC I and to TC II remained fairly constant in individual sera regardless of the amount of B_{12} added. The authors did not observe anything like the phenomenon of secondary binding described by Hall and Finkler (1966a) when large amounts of B_{12} were added. A possible explanation for this difference is that the secondary binding observed by Hall and Finkler is a loose form of binding of low avidity. This bond may have loosened in the system used by Hom and Ahluwalia.

There is experimental evidence for the *in vitro* transfer of vitamin B_{12} from intrinsic factor to TC II in the mouse (Tan and Hansen 1966). It was demonstrated in the mouse that 5—8 hours are needed after the *in vivo* saturation of TC II before serum desaturated TC II reaches normal values. Puromycin and cycloheximide inhibited the reappearance of desaturated TC II (Tan *et al.* 1967). It was further demonstrated by another technique that puromycin and cycloheximide cause a decrease of TC II in the mouse (Salhi *et al.* 1967). Rat liver perfusion experiments showed that TC II is produced in the liver (Haught *et al.* 1967).

Abnormalities in serum B_{12} binders have been described in four situations.

— In chronic myelogenous leukemia, the serum concentration of B_{12} is high and the unsaturated B_{12} binding capacity is increased. The binding capacity of TC I has been shown to be greatly increased and the binding to TC II is diminished or nil (Beard *et al.* 1954, Miller 1958, Mendelsohn *et al.* 1958, Miller and Sullivan 1959a, 1959b, Weinstein *et al.* 1959, Banerjee *et al.* 1963, Hall and Finkler 1964, 1966b, Hom *et al.* 1966, Retief *et al.* 1967b, Mikkonen *et al.* 1967).

— In polycythemia vera, a special B_{12} binding protein was described by Hall and Finkler (1967).

— In untreated pernicious anemia, the binding of added B_{12} to TC II was shown to be diminished or even absent in some cases (Hall and Finkler 1966b, Lawrence 1966). Gräsbeck (1967) confirmed that TC II is not absent in pernicious anemia. The CoB_{12} plasma clearance studies in B_{12} deficiency support the view of abnormal B_{12} binding (Hall *et al.* 1962, Hall and Finkler 1962, Meyer *et al.* 1967). All the above cited abnormalities change towards normal following the correction of B_{12} deficiency.

— In pernicious anemia patients treated with long-acting B_{12} preparations, high serum B_{12} levels and elevated serum vitamin B_{12} binding capacities were found. This was attributed to the presence of circulating IgG antibodies against TC II causing delayed plasma clearance of TC II-B_{12} complex (Schwartz and Bastrup-Madsen 1968, Olesen *et al.* 1968, Hom *et al.* 1968).

An extensive systematic study of B_{12} binders in human body fluids and blood cells was published by Simons (1964). B_{12} binding protein in human milk was studied by Finkler *et al.* (1967). A fascinating discussion concerning body B_{12} binders and their relations to each other including phylogenetic speculations, was presented by Gräsbeck (1967).

Material and Methods

Serum

Cord blood was collected from the placental parts of umbilical cords immediately after normal deliveries at the Albany Medical Center Hospital, Albany N.Y. Ten-fifteen ml of blood was taken from one placenta. The serum was separated by gentle centrifugation within four hours. It was either refrigerated for not more than 20 hours prior to use or frozen immediately after separation and stored at −20°C until used. No mildly hemolyzed samples were used. To check the possible effects of hemolysis, some grossly hemolytic serum samples were studied by DEAE-chromatography and no differences attributable to hemolysis were found.

The samples were collected from 33 normal deliveries, occurring at daytime between October 23, 1966 and June 14, 1967. Sixteen of the babies were boys and 19 girls. Their birth weights ranged from 2330 to 4490 grams, the average birth weight in the series being 3370 grams.

Large scale preparative studies were performed on pooled serum from the above mentioned cord serum samples and on cord serum obtained from Grand Island Biological Corporation, Grand Island, N.Y. (catalog number 619). This specially ordered serum was prepared in the cold, immediately frozen, shipped in the frozen stage and stored at −20°C until used. The serum was delivered in 20 ml and 50 ml lots.

Infant blood was collected at the Flower and Fifth Avenue Hospital, New York, N.Y. Three serial samples were obtained from three healthy infants at different time intervals between 1 day and 30 days. Single blood samples were collected from five healthy infants and from eleven infants hospitalized at the Flower and Fifth Avenue Hospital for various non-hematological disorders. Their ages were between 1 day and 105 days at the time of blood collection. The sera were separated and processed as described above.

Maternal blood was obtained from the mothers of seven of the above mentioned healthy infants. The maternal blood was drawn the day after the delivery. Additionally blood was obtained from four healthy women in active labor at the Albany Medical Center Hospital, right before delivery. The maternal samples were processed and stored identically with the infant and cord blood samples.

Normal adult blood was obtained from subjectively healthy male and healthy non-pregnant female laboratory personnel. Serum was separated and stored as above.

Vitamin B_{12}

The radioactive vitamin B_{12} used in this work was ^{57}Co-labeled cyanocobalamin (B.P.). It was purchased from the Radiochemical Centre Amersham, Buckinghamshire, England, through Merck and Co. Inc., Rahway N.J. Three batches with the code CT.2P were used:

Batch 37, specific activity 43 $\mu c/\mu g$ on July 20, 1966. According to the manufacturer the radiochemical purity of the batch was 93 % by dilution and electrophoretic analyses.

Batch 49, specific activity 70 $\mu c/\mu g$ on January 4, 1967. Radiochemical purity 95 %.

Batch 61, specific activity 110 $\mu c/\mu g$ on July 29, 1967. Radiochemical purity 95 %.

Aqueous dilutions, prepared from the above batches, gave working solutions with suitable concentrations of vitamin B_{12}. These working solutions were kept in the dark at +4°C and not used for more than one month after the dilution.

The non-radioactive vitamin B_{12} used in this work was USP reference standard nonradioactive cyanocobalamin.

The measurement of radioactivity

The measurement of radioactivity was done by scintillation spectrometry. A well type crystal detector connected to a scintillation spectrometer (Baird Atomic 530) with an automatic sample changer was used. The radioactivity of the samples was calculated using $^{57}CoB_{12}$ standards of corresponding volumes. Counts per minute (cpm) for the standards were recorded daily and their actual radioactivity calculated using a half life of 270 days for ^{57}Co. The counting efficiency of the system was 1.8×10^6 cpm/μc. The background varied between 20 and 40 cpm. A counting

time to provide a minimum of 1000 counts was always used for the radioactive samples, although the amount of counts recorded was usually higher

The labeling of the B_{12} binders

All the $^{57}CoB_{12}$ labeling of serum proteins was done *in vitro*. If not otherwise mentioned, the amount of radioactive vitamin B_{12} added was 300 pg per 1 ml of serum, an amount which is well within the normal unsaturated B_{12}-binding capacity of serum proteins (*e g* Miller 1958) The working solutions of $^{57}CoB_{12}$ contained 300 pg in 0 14—0.21 ml.

The radioactive vitamin was added dropwise into the serum with gentle shaking After incubating in a +37 C water bath for 30 minutes, the serum sample was dialyzed against the starting buffer of the next procedure to remove any unbound B_{12} and to equilibrate the sample. The serum sample was counted for radioactivity prior to and after the dialysis. Also the dialysing fluid was counted and no radioactivity could be detected in it when the standard amount of $^{57}CoB_{12}$ was added.

The labeled serum was then submitted for various procedures in order to fractionate the vitamin B_{12} binders and to characterize them.

DEAE-cellulose chromatography

Diethylaminoethyl (DEAE) ionic exchange cellulose type 40 was purchased from Carl Schleicher & Schuell Co, Keene N.H. The capacity of the cellulose was 0.9 meq/g The new cellulose powder was suspended in water stirred and allowed to sedimentate The yellowish supernatant containing the finest particles was decanted off This was repeated twice. The cellulose was then suspended in 0.5 N NaOH and stirred for 20—30 minutes. The alkali was washed off with water until the pH of the washing water reached 7 0 The same treatment was repeated with 0.5 N HCl and then again with 0.5 N NaOH When the last alkali had been washed off the cellulose was suspended in 0 01 M phosphate buffer pH 8.0 and the pH of the mixture brought to 8.0 with 0.3 M NaH_2PO_4 The buffer was filtered off the cellulose washed five times with 0.01 M pH 8 phosphate buffer and suspended in it. The pH was again checked and readjusted, if necessary Two-three drops of toluene per 1 liter of the mixture was added as a preservative. The cellulose was stored in the cold. Only cellulose processed from new stocks was used. DEAE-Sephadex A-50 capacity 3.9 meq/g made by Pharmacia, Uppsala, Sweden, was purchased from Pharmacia Fine Chemicals, Piscataway N.J It was processed as above using 0.5 N acid and alkali, and suspended in 0.01 M phosphate buffer pH 8.0.

The methods used for DEAE-cellulose chromatography were essentially the same as those used and described by Hall and Finkler (1965) Two modifications of the chromatography technique were used. The so called mini-column technique was used to study the B_{12} binding pattern of small serum samples, in the range of 1 ml. Columns with an internal diameter of 1 cm were packed with the DEAE-cellulose slurry in 0 01 M phosphate buffer pH 8.0. The packing was performed in 3—4 steps, first by gravity and then by applying an air pressure of ten pounds on the column. The final length of the column was 3 cm. The labeled, dialyzed serum sample was layered on the column and washed in with the starting phosphate buffer A concave phosphate buffer gradient of increasing molarity and decreasing pH, as modified by Hall and Finkler (1965) after Peterson and Chiazze (1962) was used to elute the column. To produce the gradient a nine-chambered, continuous-flow device was used. The starting buffer was 0.01 M pH 8.0 and the limiting buffer 0.3 M pH 4.5. The volume of each chamber was 25 ml. The flow rate in different columns varied between 2.5—7.0 ml/hr without any effect on the separation. Fractions of 5 ml were collected and assayed for protein and radioactivity content. The fractions from these small columns were not used for further separation or characterization of the B_{12} binders.

The so called "big column technique" of DEAE chromatography was used to process large amounts of labeled serum for further processing by other methods. DEAE-cellulose was packed to the height of 30 cm in a column with an internal diameter of 4 cm. The packing was performed in 4—5 steps, first by gravity and then by 10 pounds air pressure. Up to 50 ml labeled serum was processed with these columns. The elution gradient was the same as described for "mini-columns" the volume of each chamber being 300 ml. The experiments were performed at a temperature of +4 C with a flow rate of 30—40 ml/hr Fractions of 30—40 ml were collected and aliquots taken for protein, radioactivity and B_{12} assay The fractions were pooled according to the radioactivity distribution, concentrated by ultrafiltration and dialyzed for subsequent procedures.

CM-cellulose chromatography

Carboxymethyl (CM) ionic exchange cellulose (Whatman column chromedia CM 11 made in England by W & R Balston Ltd., nominal capacity 0.6 meq/g) was washed successively with ten volumes of 0.5 N HCl and 0.5 N NaOH. The acid and alkali were

naked off lth ater the naked cellulose as suspended i 0.02 M sodium chloride-sodium acetate buffer pH 5.4 and the pH f the mixture adjusted t 5.4. Thereafter the cellulose as rinsed several times lth the abov mentioned acetate buffer resuspended in it and stored at +4°C. N used CM cellulose as employed.

A slurry f the cellulose in 0.02 M acetat buff r pH 5.4 as poured into colum lth an internal diameter of 1.5 cm nd allowed to settle by gra ity to the height f 45 cm. The sample which had bee dialyzed gainst the same acetat buffer was layered on the column and washed in. The first elution as performed lth 0.02 M acetate buffer pH 5.4 followed by 0.027 M phosphat buffer pH 7.0, and completed lth 0.2 M phosphate buffer pH 7.8. The outlet f the column as connected to UV-scanner hich indicated the lution f the protein fractions. The buffer was changed fter the lution f protein peak.

The flow rate as kept at 60—80 ml/hr and fractions f 14 ml ere collected and counted for radioactivity. The fractions were pooled accordi g the radioactivity peaks and concentrated for further use.

Gel filtration on Sephadex[5]

Sephadex G 200 made by Pharmacia, Uppsala, Swed n, as purchased from Pharmacia Fine Chem icals, Piscata y N.J. The buffer used in the gel f ltra ion experiments as 0.05 M phosphate buffer pH 7.4 made 0.5 M for NaCl and containi g 0.02 % sodium azide as preservativ.

The gel allowed t swell in the buff for 72 hours prior t use. A slurry f it as poured to the height of 70 m in silicone coated colum with an in rnal diameter f 2.5 m. The column as stabilized ith the buffer for 4 hours. The same column was used repeatedly.

The dialyzed sample (olume 1—2 ml) as gently la ered on he column, allowed to enter and washed in th hree imes 1 ml of the gel buffer. The column as luted with the gel buffer at flow rat f 6 12 ml hr. The outlet of the colum was run hrough photoc ll recordi g the absorption at 280 mμ. Fractions of 2 ml ere collected and counted for radioacti ity. Either the UV recordi or chemical ana as employed to determine the protein con centration.

The molecula weight estimations from the gel filtration experiments ere based on the linear corre la ion b een the elution olume f molecule and he lo arithm f it molecular eight (Andrew 1964). The amount of buff needed to lut the peak fraction was taken as the elution volume of the protein. The old olume for the column was measured equally with Blue Dextran 2000 (Pharmacia). In order t eliminat the effect of possible alterations in the column during prolonged use the ratio of elution olume to oid olume as used instead of lution olume alone.

The following set of reference proteins (from Mann Research Laboratories Inc. New York, N.Y.) was used to produce the standard line illustrated in figure 1.

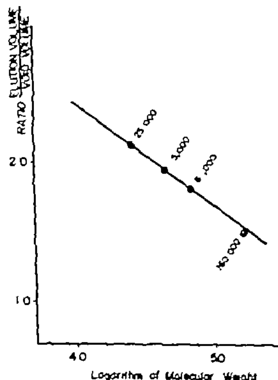


Fig. 1. The standard line used for molecular weight estimations by Sephadex G 200 gel filtration.

— Chymotrypsinogen, molecular eight 25,000
— Ovalbumin, molecular weight 45,000
Bovine albumin, molecular ight 67,000
— Human gamma globulin, molecular eight 160,000

This standard line was used t estimate molecular weight also for the filtrated samples.

Sephadex G-100 was treated similarly as G 200 and column lth the dimensions of 2.4 × 5. cm was prepared. This column was used to fractionate 1—2 ml samples f lab led serum. The protein distribution pattern recorded by the absorption at 280 mμ was used as reference to the location of the radioactivity peaks. No molecular w ight estimations were performed on this column.

time to provide a minimum of 1000 counts was always used for the radioactive samples, although the amount of counts recorded was usually higher

The labeling of the B_{12} binders

All the "CoB_{12} labeling of serum proteins was done *in vitro*. If not otherwise mentioned, the amount of radioacti e vitamin B_{12} added was 300 pg per 1 ml of serum, an amount which is well within the normal unsaturated B_{12} binding capacity of serum proteins (*e g* Miller 1958) The working solutions of "CoB_{12} contained 300 pg in 0 1—0_1 ml.

The radioactive vitamin was added dropwise into the serum with gentle shaking After incubating in a +3 C water bath for 20 minutes, the serum sample was dialyzed against the starting buffer of the next procedure, to remove any unbound B_{12} and to equilibrate the sample. The serum sample was counted for radioacti ity prior to and after the dialysis. Also the dialysing fluid was counted a d no radioactivity could be detected in it when the standard amount of "CoB_{12} was added.

The labeled serum was then submitted for various procedures in orde to fractionate the vitamin B_{12} binders and to characterize them.

DEAE-cellulose chromatography

Diethylaminoethyl (DEAE) ionic exchange cellulose type 40 was purchased from Carl Schleicher & Schuell Co, Keene N H. The capacity of the cellulose was 0.9° meq/g The new cellulose powder was suspended in water stirred and allowed to sedimentate. The yellowish supernatant containing the finest particles was decanted off. This was repeated twice. Th cellulose was then suspended in 0.5 N NaOH and stirred for "0—30 minutes. The lkali was washed off with water until the pH of th washing water reached 0. The same treatment was repeated with 0.5 N HCl and then again with 0.5 N N OH When the last alkali had been washed off the cellulose was suspended in 0.01 M phosphate buffer pH 8.0 and the pH of the mixture brought t 8.0 with 0.3 M NaH_2PO The buffer was filtered off the cellulose washed five times with 0.01 M pH 8 phosphat buffer and suspended in it. The pH was again hecked and readjusted, if necessary Two-three drops f toluene per 1 liter of the mixture was d led as a preservati n. The cellulose was stored in the cold. Only cellulose processed from new stocks was used. DEAE-Sephadex A 50, capacity 3.9 meq/g, made by Pharmacia, Uppsala Sweden, was purchased from Pharmacia Fine Chemicals, Piscataway N.J It was processed as abo using 0_ N acid and alkali, and suspended in 0.01 M phosphate buffer pH 8.0.

The methods used for DEAE-cellulose chromatography were essentially the same as those used and described by Hall and Finkler (1965) Two modifications of the chromatography technique were used. The so called "mini-column technique was used to study the B_{12} binding pattern of small serum samples, in the range of 1 ml. Columns with an internal diameter of 1 cm were packed with the DEAE-cellulose slurry in 0 01 M phosphate buffer pH 8.0. The packing was performed in 3—4 steps, first by gravity and then by applying an air pressure of ten pounds on the column. The final length of the column was 3 cm. The labeled dialyzed serum sample was layered on the column and washed in with the starting phos phate buff A concave phosphate buffer gradient f increasing molarity and decreasing pH, as modified by Hall and Finkler (1963) after Peterson and Chiazze (1962) was used to elute the column. To produce the gradient a nine-chambered, continuous-flow device was used. The starting buffer was 0.01 M pH 8.0 and the limiting buffe 0.3 M pH 4.5. The volume of each chamber was _3 ml. The flow rate in different columns varied between _5— ,0 ml/hr without any effect on the separation. Fra tions of 3 ml were collected a d assayed for protein and radioacti ity content. The fractions from these small columns were not used fo further separation or characterization of the B_{12} binders.

The so called "big column technique of DEAE chromatography was used to process large amounts of labeled serum fo further processing by other methods. DEAE-cellulose was packed to the height of "0 cm in a column with a internal diameter of 4 cm. The packing was pe formed in 4—3 steps, first l gravity and then by 10 pound air pressure. Up t 30 ml labeled serum was processed ith these columns. The l tion gradient was the same as described for "mini-columns the olume of each hamber being 300 ml. The experime t w re performed at a temperature of +4 C with a flow rate f 30—40 ml/hr Fractions of 30—40 ml were collected and aliquots tak n f r protein, radioa tivit nd B_{12} assa The fra tions were pooled according to the radioactivity distribution, concentrated by ultrafiltratio nd dialyzed fo subsequent procedures.

CM-cellulose chromatography

Carboxymethyl (CM) ionic xchange cellulose (Whatman column hromedia CM 11 made in England by W & R Balston Ltd., nominal capacity 0.6 meq/g) was washed successi ely with ten olumes of 0.5 N HCl and 0.5 N N OH The acid and alkali were

ashed off ith ater the ashed cellulose as suspended in 0.03 M sodium hloride-sodium acetat buffer pH 5.4, and the pH f the mixture adjusted t 5.4. Thereafter the cellulose as rinsed several times ith the bov mentioned acetate buffer resuspended in it and stored at +4 C. N used CM cellulose as employed.

A slurry of the cellulose in 0.03 M acetat buffer pH 5.4 as poured into column ith an internal diameter f 1.5 cm and allowed t settle by gra ity t the height of 43 cm. The sample hich had been dialyzed against the same acetat buffer was layered on the column and ashed in. The first elution as performed ith 0.03 M acetat buffer pH 5.4, followed by 0.027 M phosphat buffer pH 7.0, and completed ith 0.2 M phosphate buffer pH 7.8. The outlet of the column was connected t UV-scanner hich indicated the elution of the protein fractions. The buffer as changed fter the elution of protein peak.

The flow rate as kept at 60—60 ml/hr nd fractions f 14 ml ere collected and counted for radioacti ity. The fractions ere pooled according t the radioactivity peaks and concentrated for further use.

Gel filtration on Sephadex®

Sephadex G-200 made by Pharmacia, Uppsala, Sweden, as purchased from Pharmacia Fine Chem icals, Piscata y N.J. The buffer used in the gel filtration experiments as 0.03 M phosphate buffer pH 7.4, made 0.8 M for NaCl and containing 0.0? % sodium azide as preservati.

The gel as allowed t swell in the buffer for 72 hours prior t use. A slurry f it as poured t the height f 70 cm in silicone coated column ith an internal diameter of 2.5 cm. The olumn as stabilized ith the buffer for 4 hours. The same column as used repeatedly.

The dialyzed sample (olume 1—3 ml) as gently layered on the column, allowed t enter and washed in with three times 1 ml of the gel buffer. The column was eluted th the gel buffer at flow rat f 6—12 ml/hr. The outlet f the colum was run through photocell recording the absorption t 280 mμ. Fractions f 2 ml ere collected nd counted for radioacti ity. Either the UV recorder or hemical was as employed t determine the protein con centration.

The molecular eight estimations from the gel filtration experiments were based on the linear corre lation between the elution olume f molecule and the logarithm of its molecular eight (Andrews 1964). The amount of buffer needed to lut the peak fraction as taken as the lution olume f the protein. The oid olume for the column was measured equally with Blue Dextran 2000 (Pharmacia). I order t liminate the ffect of possible alterations in the colum during prolonged use the ratio f elution olume t oid olume as used instead f elution olume alone.

The following set f reference proteins (from Mann Research Laboratories Inc. New York, N.Y.) as used t produce the standard line illustrated in figure 1.

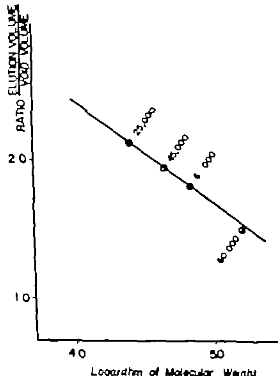


Fig. 1. The standard line used for molecular eight estimations by Sephadex G 200 gel filtration.

— Chymotrypsinogen, molecular eight 25,000
— Ovalbumin, molecular eight 45,000
— Bovine albumin, molecular eight 67,000
— Human gamma globulin, molecular eight 100,000

This standard line as used t estimat molecular eight alues for the filtrated samples.

Sephadex G-100 was treated similarly as G-200 and column ith the dimensions f 2.4 × 65 cm as prepared. This column was used to fractionate 1—8 ml samples f lal led serum. The protein distribution pattern recorded by the absorption t 280 mμ as used as reference t the location of the radio-acti ity peaks. N molecular eight estimations ere performed on this olumn.

time to provide a minimum of 1000 counts was always used for the radioactive samples, although the amount of counts recorded was usually higher

The labeling of the B , binders

All the $^{57}CoB_{12}$ labeling of serum proteins was done *in vitro*. If not otherwise mentioned, the amount of radioactive vitamin B_{12} added was 300 pg per 1 ml of serum, an amount which is well within the normal unsaturated B_{12} binding capacity of serum proteins (*e g* Miller 1958) The working solutions of $^{57}CoB_{12}$ contained 300 pg in 0 14—0.21 ml.

The radioactive vitamin was added dropwise into the serum with gentle shaking After incubating in a +37 C water bath for 20 minutes, the serum sample was dialyzed against the starting buffer of the next procedure, to remove any unbound B_{12} and to equilibrate the sample. The serum sample was counted for radioactivity prior to and after the dialysis. Also the dialyzing fluid was counted and no radioactivity could be detected in it when the standard amount of $^{57}CoB_{12}$ was added.

The labeled serum was then submitted for various procedures in order to fractionate the itamin B_{12} binders and to characterize them.

DEAE-cellulose chromatography

Diethylaminoethyl (DEAE) ionic exchange cellulose type 40 was purchased from Carl Schleicher & Schuell Co, Keene N H. The capacity of the cellulose was 0.92 meq/g The new cellulose powder as uspe ded in water stirred and allowed to sedimentate. The yellowish supernatant containing the finest particles was decanted off This was repeated twice. The cellulose was then suspended in 0.5 N NaOH an l stirred for 20—30 minutes. The alkali was washed off with water until the pH f the washi g w t reached 7.0 The same treatment was repeated with 0.5 N HCl and then gain with 0.5 N NaOH When the last alkali had been washed off the cell lose was suspended in 0.01 M phosphate buffer pH 8.0 and the pH of the mixture brought to 8.0 with 0.3 M NaH_2PO The buffer was filtered off the cellulose washed five times with 0.01 M pH 8 phosphat buffer and suspended in it. The pH was agai hecked and readjusted, if necessary Two-three drops of toluene per 1 liter of the mixture was added as a preservative. The cellulose was stored in the cold. Only cellulose processed from new stocks was used. DEAE-Sephadex A 50 capacity 3.9 meq/g, made by Pharmacia, Uppsala, Sweden, was purchased from Pharmacia F ne Chemicals, Piscataway N.J It was processed as abo e using 0.5 N acid and alkali and uspended i 0.01 M phosphate buffer pH 8.0.

The methods used for DEAE-cellulose chromatography were essentially the same as those used and described by Hall and Finkler (1963) Two modifications of the chromatography technique were used. The so called mini-column technique" was used to study the B_{12} binding pattern of small serum samples, in the range of 1 ml. Columns with a internal diameter of 1 cm were packed with the DEAE-cellulose slurry in 0.01 M phosphate buffer pH 8.0. The packing was performed in 3—4 steps, first by gra ity and then by applying an air pressure of ten pounds on the column. The final length of the column as 3 cm. The labeled, dialyzed serum sample was layered on the column and washed in with the starting phosphate buffer A concav phosphate buffer gradient of increasing molarity and decreasi g pH as modified by Hall and Finkler (1963) after Peterson and Chiazze (1962) was used to elute the column. To produce the gradient a nine-chambered, continuous-flow device was used. The starting buffer was 0.01 M pH 8.0 and the limiting buffer 0.3 M pH 4.5 The volume of each chamber was 25 ml. The flow rate in different columns varied between 5—7.0 ml/hr witho t any effect on the separation. Fractions of 3 ml were collected and assayed for protein and radioactivity co tent The fractions from these small columns w re not used for further separation or characterization of the B_{12} binders.

The so called "big column technique" of DEAE-chromatography was used to process large amounts of labeled serum for further processing by other methods. DEAE-cellulose was packed t the height of 20 cm in a column with an int rnal diameter of 4 cm. The packing was performed in 4— steps, first by gra ity and then l 10 pound air pressure. Up t 50 ml labeled serum was processed with these columns. The el tio gradient was the same as described for "mini-columns" the lume of each hamber being 300 ml. The experiment ere performed at a temperature of +4 C with a flow rat of 30—40 ml/hr Fra tions of 30—40 ml were collected and aliquots t ken f r p ot i radioactivity a l B_{12} assay The fractions ere pooled according to the radioacti ity distribution, concentrated by ultrafiltration and dialyzed for subsequent procedures.

CM-cellulose chromatography

Ca boxymethyl (CM) ionic xchange cellulose (Whatman column chromedia CM 11 made in England by W & R Balston Ltd., nominal capacity 0.6 meq/g) was washed successi ely with t ol mes f 0.5 N HCl and 0.5 N NaOH. The H d alkali were

ashed ff with water the washed cellulose was suspended in 0.02 M sodium chloride-sodium acetate buffer pH 5.4, and the pH of the mixture adjusted t 5.4. Thereafter the cellulose as rinsed several times with the abov mentioned acetate buffer resuspended in it and stored at +4 C. No used CM cellulose was employed.

A slurry f the cellulose in 0.02 M acetate buffer pH 5.4 as poured into column ith an internal diameter f 1.5 cm and allowed t settle by gra ity to the height of 45 cm. The sample which had been dialyzed against the same acetat buffer was layered on the column and washed in. The first elution as performed with 0.02 M acetat buffer pH 5.4, followed by 0.027 M phosphate buffer pH 7.0, and completed with 0.2 M phosphat buffer pH 7.8. The outlet of the column as connected to UV-scanner hich indicated the elution of the protein fractions. The buffer as changed after the elution f protein peak.

The flow rate was kept t 60—50 ml/h and fractions of 14 ml ere collected and counted for radioactivity The fractions were pooled according t the radioactivity peaks and concentrated for further use

Gel filtration on Sephadex®

Sephadex G-200 made by Pharmacia, Uppsala, Sweden, as purchased from Pharmacia Fine Chemicals, Piscataway N J. The buffer used in the gel filtration experiments as 0.03 M phosphat buffer pH 7.4 made 0.5 M for NaCl and containing 0.02 % sodium azide as preservativ

The gel as allowed to swell in the buffer for 72 hours prior to use. A slurry f it was poured to the height of 70 cm in silicone coated column with an internal diameter f 2.5 cm The column was stabilized with the buffer for 24 hours. The same column was used repeatedl

The dialyzed sample (olume 1—2 ml) as gently la ered on the column, allowed t enter and ashed in ith three times 1 ml of the gel buffer The column was eluted ith the gel buffer t flow rate f 6—12 ml/hr The outlet of the column as run through photocell recording the absorption at 280 mμ Fractions of 2 ml ere collected and counted for radioactivity Either the UV-recorder or chemical assay as employed t determine the protein concentration.

The molecular eight estimations from the gel filtration experiments were based on the linear correlation between the elution olume of molecule and the logarithm f its molecular eight (Andrews 1964) The amount of buffer needed to lute the peak fraction was taken as the elution olume of the protein. The old olume for the column was measured equally with Blue Dextran 2000 (Pharmacia) In order t eliminate the effect f possible alterations in the column during prolonged use the ratio f elution olume t old olume was used instead of elution olume alone.

The following set f reference proteins (from Mann Research Laboratories Inc., New York, N Y) was used t produce the standard line illustrated in figure 1

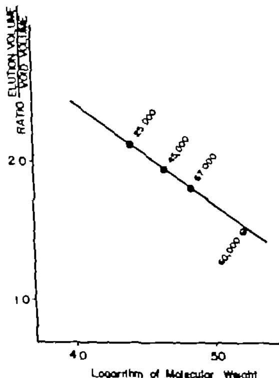


Fig 1. The standard line used for molecular eight estimations by Sephadex G 200 gel filtration.

— Chymotrypsinogen, molecular eight 25,000
— Ovalbumin, molecular weight 45,000
— Bovine albumin, molecular eight 67,000
— Human gamma globulin, molecular weight 160,000

This standard line as used t estimate molecular eight also for the filtrated samples.

Sephadex G-100 was treated similarly as G 200 and column with the dimensions of 2.4 × 85 cm was prepared. This column was used to fractionate 1—2 ml samples of labeled serum. The protein distribution pattern recorded by the absorption at 280 mμ was used as reference to the location f the radioactivity peaks. N molecular eight estimations ere performed on this column.

Electrophoresis

Geon block electrophoresis was performed using essentially the same methods as Hall and Finkler (1962) Geon numbe 4?7 polyvinylchloride resin was purchased from B. F Goodrich Co., Niagara Falls, N Y The buffers used were 0.06 M barbiturate buffer pH 8.6 and 0 1 M sodium acetate-sodium chloride buffer pH 4.5.

The resin was suspended in water stirred and filtered. The same treatment was repeated twice using the buffer A wet semi firm slurry was made with the buffer and poured into three, separated, parallel blocks of 45 cm × 8 cm × cm in the electrophoretic apparatus. The gel was connected to the buffer compartments with well soaked gauze bridges. The samples (CM purified binders or in some instances labeled serum) were dialyzed against the electrophoresis buffer and applied at the center of the block in a transverse slit of about 2—3 mm. The volume of the sample varied between 0.—0.5 ml, depending on the level of concentration achieved by the preceeding ultrafiltration d judged by the radioactivity of the sample The starting voltage was 200 V (= 4.4 V/cm) and the running time 18—?0 hours. The block was kept at a temperature of +4 C by a built in cooling system in the electrophoretic apparatus. After the run the block was dried for 1—1.5 hours and then cut into 16 transverse segment of 1 cm. Each segment was counted for radioactivity and the total cpm per segment recorded. The distance from the point of application for the segment containing the highest amount of cpm was taken as the mobility of the fraction. The electrophoretically separated fractions were not used for further tudies. The distribution of serum proteins recorded in a few experiments was measured by lating the segments with 0.01 M phosphate buffer pH 8.0 and assaying the eluates for protein.

Uptake of ' CoB by HeLa cells

The technique used was essentially the same as that described by Finkler and Hall (1967) HeLa cells in monolayer cultures were generously provided by Dr J V Landau, Ph.D the Biology Section of Veterans Administration Hospital, Albany N Y The cell growth medium was decanted off and the dialyzed sample (CM purified binders in a volume of 1—3 ml) with Hank's base 199-IX (from Grand Island Biol ogical Corporation, Grand Island, N Y catalog number 115 H) was added to the cells in a total volume of 12 ml. The cell bottles were then placed at +37°C for 2 hrs. After the incubation the medium was decanted off and the cell layers washed twice with buffered, ice cold solution containing 0.8 % NaCl, 0.04 % KCl, 0.1 % dextrose and 0.035 g NaHCO₃. The cells were then scraped from the bottle with a rubber tipped spatula and washed three times with centrifugation in the ice-cold buffered saline solution. The washed cells were suspended in 5 ml of the same solution. The amount of cells was counted in a hemocytometer using the standard laboratory technique for leukocyte counting The cell suspension was counted fo radioactivity

Assay of vitamin B ₁

The assays of vitamin B_{12} were kindly performed by Mr Edward B. Allen, using the *Euglena gracilis* strain and the method described in detail by Hall and Allen (1964)

Concentration of the samples

The fractions o pooled fractions from the chromatographic procedures were concentrated for further use by ultrafiltrating them through Visking dialysis tubing (obtained from Union Carbide Corporation, Chicago, Ill.) The tubing was thoroughly washed, filled with the sample, and placed into reduced pressure in a vacuum flask at +4 C. The inside of the tubing was kept in open connection with the outside air The reduced pressure was adjusted to a le l which ga e maximal expansion of the tubing without breaking it. Possible leaks were detected by counting the ultrafiltered outside fluid for radio ecti ity

Dialysis

The dialysis of the samples against the appropriate buffer was performed in bags of Visking dialysis tubing. For DEAE-chromatography on "mini-columns" a short dialysis of 1—2 h urs against 250 ml of the buffer was used. For other purposes the samples were dialyzed three successi e times against 30—40 f ld volumes and fo 16— 4 hours. Dialysis was performed at +4 C and a magnetic stirrer was used t mix the fluid.

Protein determination

The protein concentration in the chromatography fractions was measured by the method f Lowry t al (1951) The protein distribution was used as refer ence t th location f the radioacti ity peaks. Hence only the optical densities from the photom te were ecorded and the ctual protein concentrations were not calculated.

All the reagents used in the present work were f Anala Grade" quality

Results

The binding of added B_{12} in normal adult serum

Twenty samples of normal adult serum were studied adding 300 pg of ^{57}Co-labeled B_{12} per 1 ml of serum and using the mini-column technique of DEAE-chromatography. The main binding of added B_{12} in the chromatograms was just before the main protein peak, i.e. in the TC II region (Hall and Finkler 1965). In addition to the main TC II-peak of radioactivity there was some binding of CoB$_{12}$ to proteins eluted later from the column. The carrier of circulating native B_{12}, TC I is known to be eluted after the bulk of protein (Hall and Finkler 1965) and a small amount of added B was found bound to it. A varying amount of added B_{12} was eluted in between these two regions. This amount was always a minor one and the complex was not characterized further. Figures 2 and 3 show the variation in the binding of small amounts of added B_{12} in the middle region of the chromatograms.

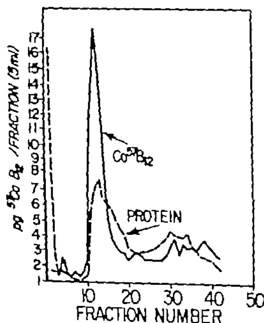


Fig. 2. DEAE-cellulose chromatogram of 1 ml of normal adult serum with 300 pg ^{57}CoB$_{12}$. The peak of TC II is in fraction number 12, TC I is located in fractions 37—44.

The binding of added B_{12} in cord serum

Ten different samples of cord serum were studied using the same technique as above. Three peaks of radioactivity could be consistently detected in the chromatograms. The first peak was located just prior to the main protein peak and thus corresponded to TC II

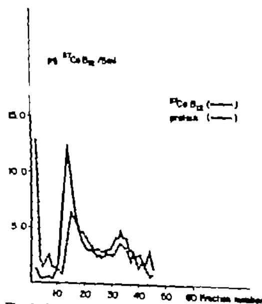


Fig. 3. DEAE cellulose chromatogram of 1 ml of normal adult serum with 300 pg ^{57}CoB$_{12}$.

Electrophoresis

Geon block electrophoresis was performed using essentially the same methods as Hall and Finkler (1963). Geon number 427 polyvinylchloride resin was purchased from B. F. Goodrich Co., Niagara Falls, N.Y. The buffers used were 0.06 M barbiturate buffer pH 8.6 and 0.1 M sodium acetate-sodium chloride buffer pH 4.5.

The resin was suspended in water, stirred and filtered. The same treatment was repeated twice using the buffer. A wet, semi firm slurry was made with the buffer and poured into three separated, parallel blocks of 45 cm × 8 cm × 2 cm in the electrophoretic apparatus. The gel was connected to the buffer compartments with well soaked gauze bridges. The samples (CM purified binders or in some instances labeled serum) were dialyzed against the electrophoresis buffer and applied at the center of the block in a transverse slit of about —3 mm. The volume of the sample varied between 0.2—0.5 ml depending on the level of concentration achieved by the preceding ultrafiltration and judged by the radioactivity of the sample. The starting voltage was 200 V (= 4.4 V/cm) and the running time 18—20 hours. The block was kept at a temperature of +4 C by a built in cooling system in the electrophoretic apparatus. After the run the block was dried for 1—1.5 hours and then cut 1 to 10 transverse segments of 1 cm. Each segment was counted for radioactivity and the total cpm per segment recorded. The distance from the point of application for the segment containing the highest amount of cpm was taken as the mobility of the fraction. The electrophoretically separated fractions were not used for further studies. The distribution of serum proteins recorded in a few experiments was measured by eluting the segments with 0.01 M phosphate buffer pH 8.0 and assaying the eluates for protein.

Uptake of CoB_{12} by HeLa cells

The technique used was essentially the same as that described by Finkler and Hall (1967). HeLa cells in monolayer cultures were generously provided by Dr. J. V. Landau, Ph.D., the Biology Section of Veterans Administration Hospital, Albany, N.Y. The cell growth medium was decanted off and the dialyzed sample (CM purified binders in a volume of 1— ml) with Hank's base 199-IX (from Grand Island Biological Corporation, Grand Island, N.Y., catalog number 115 H) was added to the cells in a total volume of 12 ml. The cell bottles were then placed at +37 C for 2 hrs. After the incubation the medium was decanted off and the cell layers washed twice with buffered, ice-cold solution containing 0.8 % NaCl, 0.04 % KCl, 0.1 % dextrose and 0.033 % $NaHCO_3$. The cells were then scraped from the bottle with a rubber-tipped spatula and washed three times with centrifugation in the ice-cold buffered saline solution. The washed cells were suspended in 5 ml of the same solution. The amount of cells was counted in a hemocytometer using the standard laboratory technique for leukocyte counting. The cell suspension was counted for radioactivity.

Assay of vitamin B_{12}

The assays of vitamin B_{12} were kindly performed by Mr. Edward S. Allen, using the *Euglena gracilis z* strain and the method described in detail by Hall and Allen (1964).

Concentration of the samples

The fractions or pooled fractions from the chromatographic procedures were concentrated for further use by ultrafiltrating them through Visking dialysis tubing (obtained from Union Carbide Corporation, Chicago, Ill.). The tubing was thoroughly washed, filled with the sample and placed in reduced pressure in a vacuum flask at +4 C. The inside of the tubing was kept in open connection with the outside air. The reduced pressure was adjusted to level which gave maximal expansion of the tubing without breaking it. Possible leaks were detected by counting the ultrafiltered outside fluid for radioactivity.

Dialysis

The dialysis of the samples against the appropriate buffer was performed in bags of Visking dialysis tubing. For DEAE chromatography on mini-columns a short dialysis of 1—2 hours against 250 ml of the buffer was used. For other purposes the samples were dialyzed three successive times against 30—40 fold volumes and for 16—24 hours. Dialysis was performed at +4 C and a magnetic stirrer was used to mix the fluid.

Protein determination

The protein concentration in the chromatography fractions was measured by the method of Lowry et al. (1951). The protein distribution was used as a reference to the location of the radioactivity peaks. Hence, only the optical densities from the photometer were recorded, and the actual protein concentrations were not calculated.

All the reagents used in the present work were of "Analar Grade" quality.

Results

The binding of added B_{12} in normal adult serum

Twenty samples of normal adult serum were studied adding 300 pg of ^{57}Co-labeled B_{12} per 1 ml of serum and using the mini-column technique of DEAE-chromatography. The main binding of added B_{12} in the chromatograms was just before the main protein peak, i.e. in the TC II region (Hall and Finkler 1965). In addition to the main TC II peak of radioactivity there was some binding of CoB$_{12}$ to proteins eluted later from the column. The carrier of circulating native B_{12}, TC I, is known to be eluted after the bulk of protein (Hall and Finkler 1965) and a small amount of added B_{12} was found bound to it. A varying amount of added B_{12} was eluted in between these two regions. This amount was always a minor one and the complex was not characterized further. Figures 2 and 3 show the variation in the binding of small amounts of added B_{12} in the middle region of the chromatograms.

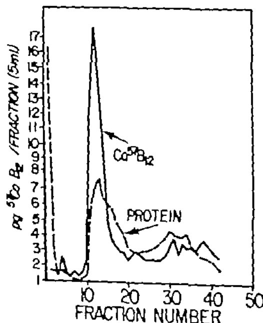


Fig. 1. DEAE-cellulose chromatogram of 1 ml of normal adult serum with 200 pg CoB$_{12}$. The peak of TC II is in fraction number 12, TC I is located in fractions 27—40.

The binding of added B_{12} in cord serum

Ten different samples of cord serum were studied using the same technique as above. Three peaks of radioactivity could be consistently detected in the chromatograms. The first peak was located just prior to the main protein peak and thus corresponded to TC II.

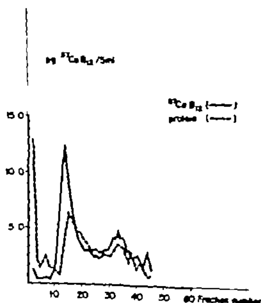


Fig. 2. DEAE-cellulose chromatogram of 1 ml of normal adult serum with 300 pg ^{57}CoB$_{12}$.

Electrophoresis

Geon block electrophoresis was performed using essentially the same methods as Hall and Finkler (1962) Geon number 4?7 polyvinylchloride resin was purchased from B F Goodrich Co., Niagara Falls, N Y The buffers used were 0.06 M barbiturate buffer pH 8.6 and 0 1 M sodium acetate-sodium chloride buffer pH 4.5.

The resin was suspended in water stirred and filtered. The same treatment was repeated twice using the buffer A wet semi firm slurry was made with the buffer and poured into three separated, parallel blocks of 45 cm × 8 cm × 2 cm in the electrophoretic apparatus. The gel was connected to the buffer compartments with w ll soaked gauze bridges. The samples (CM purified binders or in some instances labeled serum) were dialyzed against the electrophoresis buffer and applied at the center of the block in a transverse slit of about 2—3 mm. The volume of the sample varied between 0.2—0.5 ml, depending on the level of concentration achieved by the preceding ultrafiltration and judged by the radioactivity of the sample. The starting voltage was 200 V (= 4.4 V/cm) and the running time 18—20 hours. The block was kept at a temperature of +4 C by a built in cooling system in the electrophoretic apparatus. After the run the block was dried for 1—1.5 hours and then cut into 10 transverse segments of 1 cm. Each segment was counted for radioactivity and the total cpm per segment recorded. The distance from the point of application to the segment containing the highest amount of cpm was taken as the mobility of the fraction. The electrophoretically separated fractions were not used fo further studies. The distribution of serum proteins recorded in a few experiments was measured by eluting the segments with 0.01 M phosphate buff r pH 8.0 and assaying the eluates for protein.

Uptake of CoB by HeLa cells

The technique used was essentially the same as that described by Finkler and Hall (1967) HeLa cells in monolayer cultures were generously provided by Dr J V Landau, Ph.D the Biology Section of Veterans Administration Hospital, Albany N Y The cell growth medium was decanted off and the dialyzed sample (CM purified binders in a volume of 1—2 ml) with Hank's base 199-IX (from Grand Island Biol ogical Corporation, Grand Island, N Y catalog number 115 H) was added to the cells in a total volume of 13 ml. The cell bottles were then placed at +37°C for 3 hrs. After the incubation the medium was decanted off and the cell layers washed twice with buffered, ice-cold solution containing 0.8 % NaCl, 0.04 % KCl, 0.1 % dextrose and 0.035 % $NaHCO_3$. The cells were then scraped from the bott with a rubber-tipped spatula and washed three tim with centrifugation in the ice-cold buffered salin solution. The washed cells were suspended in 5 m of the same solution. The amount of cells was counte in a hemocytometer using the standard laborator technique for leukocyte counting The cell suspensio was counted for radioactivity

Assay of vitamin B_{12}

The assays of vitamin B_{12} were kindly performed b Mr Edward S. Allen, using the *Euglena gracilis* strain and the method described in detail by Hal and Allen (1964)

Concentration of the samples

The fractions or pooled fractions from the chromato graphic procedures were concentrated for further u by ultrafiltrating them through Visking dialys tubing (obtained from Union Carbide Corporation Chicago, Ill.) The tubing was thoroughly ashed filled with the sample and placed into reduce pressure in a vacuum flask at +4 C. The inside o the tubing was kept in open connection with the outside air The reduced pressure was adjusted to a level which gave maximal expansion of the tubing without breaking it. Possible leaks w re detected by counting the ultrafiltered outside fl id for radio acti ity

Dialysis

The dialysis of the samples gainst the appropriate buffer was performed in bags of Visking dialysis tubing For DEAE hromatography on mini-columns a short dialysis f 1—3 h urs gainst 250 ml of the buffer was used. For other purposes the samples were dialyzed three successi times against 30—40 fold volumes and for 10— 4 hours. Dialysis was performed at +4 C and a magnetic stirrer was used to mix the fluid.

Protein determination

The protein concentratio in the chromatography fractions was measured by the method of Lowry et al. (1951) The protein distributio was used as a ref ence to the location of the radioacti it peaks Hence, only the ptical densities from the photom eter were recorded nd the tual protein con centrations were not calculated.

All the reagents used in th present ork re of Analar Grade" qualit

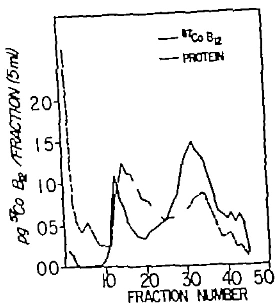


Fig 7 DEAE-cellulose chromatogram of 1 ml f cord serum with 50 pg $^{57}CoB_{12}$

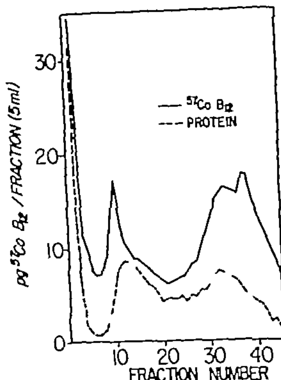


Fig 9. DEAE cellulose chromatogram f 1 ml of cord serum with 1000 pg $^{57}CoB_{12}$ 72 % f the added labeled vitamin B was bound.

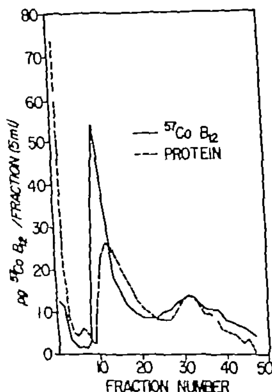


Fig. 8. DEAE-cellulose chromatogram f 1 ml of cord serum ith 1000 pg $^{57}CoB_{12}$ 88 % of the added labeled vitamin B_{12} was bound.

from the 1000 pg/ml experiments. The amounts of added B_{12} boun l in these ex periments were 88 % and % respectively

The binding of added B in infant serum

Twenty five serum samples from infants ranging in age from 1 to 158 days were studied using the "mini-column technique of DEAE-chromatography. Although the level of separation did not permit quantitated comparisons between the different chromatograms, the binding to FTC was easily detected and roughly graded as strong, moder ate, or slight as compared to the binding to TC II. Table 1 presents the list of these chromatograms. The youngest infant whose serum did not give the cord serum pattern was 10 days old. On the other hand, a sample taken from a 106 days old infant still con-

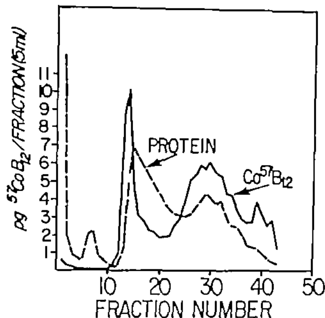


Fig 4 DEAE-cellulose chromatogram of 1 ml of cord serum with 300 pg CoB₁₂. The peak fractions for *TC II FTC and TC I are 14 30 and 39 respectively*

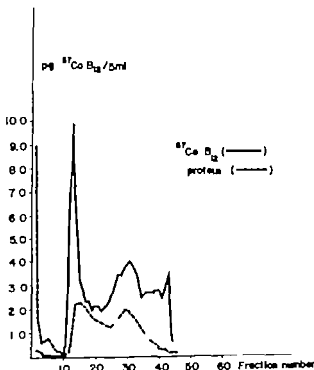


Fig 5. DEAE-cellulose chromatogram of 1 ml of cord serum with 300 pg $^{57}CoB_{12}$.

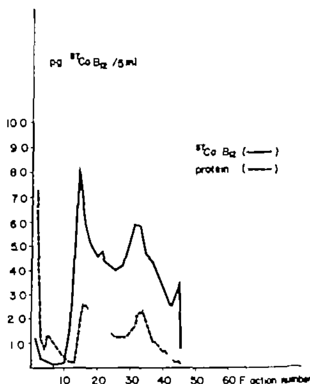


Fig 6. DEAE-cellulose chromatogram of 1 ml of cord serum with 300 pg $^{57}CoB_{12}$.

The third peak, which contained the least amount of $^{57}CoB_{12}$, was at the end of the chromatogram in the TC I region The second peak in between these two was located corresponding to the minor uncharacterized binder in adult chromatograms. It occurred in all the samples studied Figure 4 shows a typical chromatogram of cord serum with 300 pg of labeled B added per 1 ml. Figures 5 and 6 show the variation in the amounts of added B bound to TC II and to the middle binder which will be referred to as the fetal transcobalamin FTC

Five samples of cord serum were studied adding small amounts of labeled B to the serum. One sample was studied with an addition of 30 pg/ml two with 50 pg/ml and two with 100 pg/ml In all of these a definite peak of radioactivity was found in the FTC region. Figure 7 shows a chromatogram of cord serum with 50 pg of labeled B per 1 ml

To four cord serum samples 1000 pg of labeled B_{12} was added per 1 ml and the samples were submitted to chromatography as above *Under these conditions the added B* was not completely bound and the percentages of binding were 54 65 72 and 88 % Figures 8 and 9 show two types of chromatograms

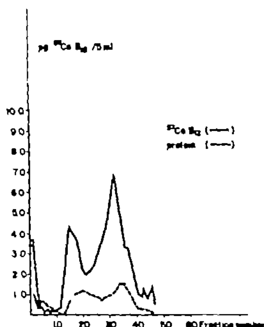


Fig. 10 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Age one day Experiment number 2 in table 1

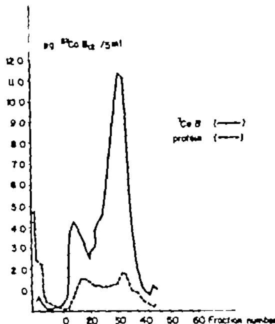


Fig. 12 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg CoB_{12}. Baby M age three days. Experiment number 5 in table 1

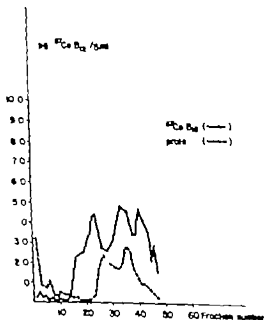


Fig 11 DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Baby R., age three days. Experiment number 4 in table 1.

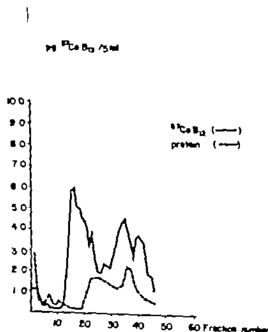


Fig. 13. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Baby R., age eight days. Experiment number 6 in table 1.

Table 1 *DEAE-chromatograms of infant serum samples*

Experiment number	Age (days)	Binding of added B_{12} to FTC	Figure	Binding of added B_{12} to the FTC-like binder in the mother
1	1	strong		strong
	1	strong	10	strong
3	3	strong		strong
4	3	strong	11	intermediate
5	3	strong	12	intermediate
6	8	moderate	13	intermediate
7	10	slight	14	absent
8	10	moderate		absent
9	11	strong		intermediate
10	11	strong		strong
11	17	moderate	15	intermediate
12	30	moderate		strong
13	30	moderate	16	intermediate
14	35	strong		
15	4[illegible]	slight		
16	46	moderate		
17	53	slight		
18	54	strong		
19	69	slight		
20	77	strong		
21	80	strong		
22	86	slight	17	
23	90	slight		
24	106	moderate	18	
25	158	slight		

tained a definite binder with the chromatographic properties of FTC Illustrative examples of the different infant serum chromatograms can be seen in figures 10 through 18.

Some of the 25 samples were drawn from the same infants at different ages. Table 2 gives a summary of these chromatograms. Figures 11 13 and 16 and figures 12 and 15 illustrate the changing pattern of B_{12} binding in these serial samples.

Table 2. *DEAE-chromatograms of serial infant samples*

Name	Experiment number (table 1)	Age (days)	Binding to FTC	Figure
Baby V	1	1	strong	
	3	3	strong	
	12	30	moderat	
Baby R.	4	3	strong	11
	6	8	moderat	13
	13	30	moderate	16
Baby M.	5	3	strong	12
	9	11	strong	
	11	17	moderate	15

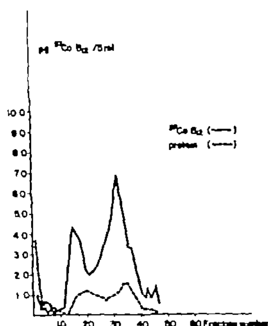


Fig. 10. DEAE-cellulose chromatogram f 1 ml f infant serum with 300 pg $^{57}CoB_{12}$. Age one day. Experiment number 2 in table 1.

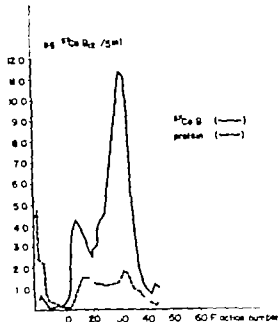


Fig. 1.. DEAE-cellulose chromatogram of 1 ml f infant serum with 300 pg $^{57}CoB_{12}$. Baby M., age three days. Experiment number 5 in table 1.

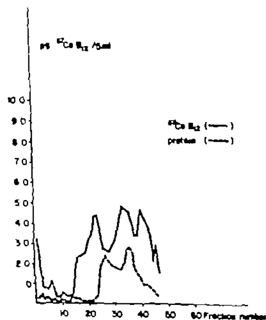


Fig. 11. DEAE-cellulose chromatogram f 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Baby E., ge three da s. Experiment number 4 in table 1.

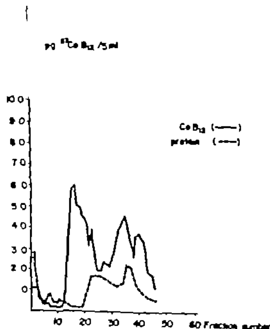


Fig. 12. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg CoB$_{12}$. Baby E., age eight days. Experiment number 6 in table 1.

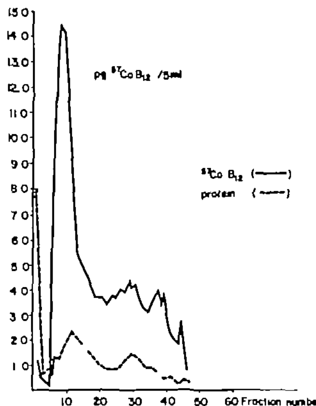


Fig 14. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Age ten days. Experiment number 7 in table 1

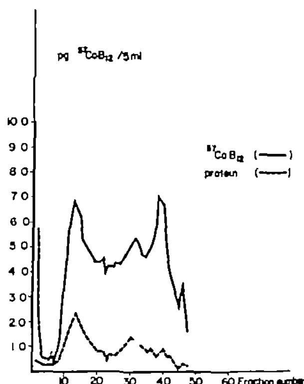


Fig 16. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Baby R., age 30 days. Experiment number 13 in table 1

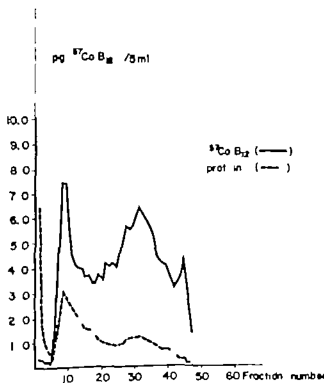


Fig 15. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Baby M., age 17 days. Experiment number 11 in table 1

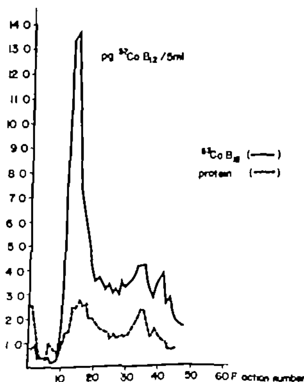


Fig 17. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg $^{57}CoB_{12}$. Age 86 days. Experiment number 23 in table 1

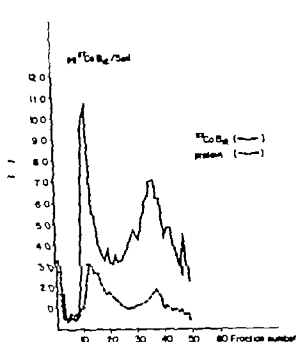


Fig. 18. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg ^{57}CoB$_{12}$. Age 105 days. Experiment number 24 in table 1.

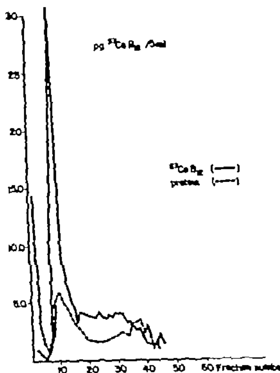


Fig. 19. DEAE-cellulose chromatogram of 1 ml of serum from delivering mother with 300 pg ^{57}CoB$_{12}$. Experiment number 8 in table 1 is of the child of this mother.

The binding of added B_{12} in maternal serum

Sera from twelve delivering or newly delivered mothers were studied by DEAE-chromatography. Three of the samples gave the classical adult binding pattern with almost all of the added B_{12} bound to TC II. In five samples a small peak of radioactivity was found corresponding to the location of FTC. However this peak was not larger than that found in some of the normal adult samples. In the remaining four samples a considerable amount of the added B_{12} was bound to the FTC-like binder and the chromatograms of these cases were indistinguishable from the cord serum chromatograms. Figures 19, 20 and 21 illustrate the three different types of maternal chromatograms. All three types of chromatograms were obtained both in the pre-delivery and in the post delivery group of samples. The type of the maternal B_{12} binding pattern for the studied paired mother-child samples is given in Table 1.

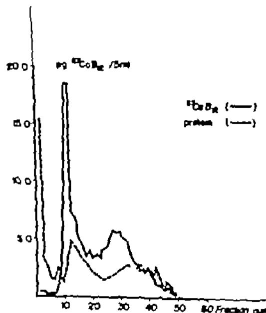


Fig. 20. DEAE-cellulose chromatogram of 1 ml of serum from delivering mother with 300 pg ^{57}CoB$_{12}$. Experiments number 4, 8 and 13 in table 1 and ...

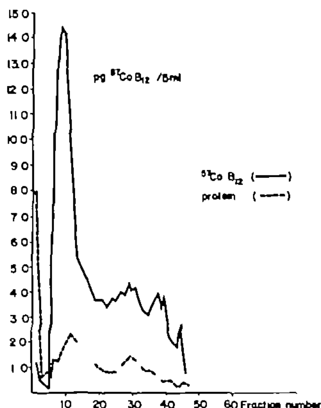


Fig 14. DEAE-cellulose hromatogram of 1 ml of infant serum with 300 pg ^{57}CoB$_{12}$. Age ten days. Experiment number 7 in table 1

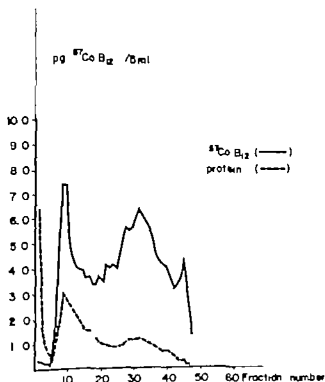


Fig 15. DEAE-cellulose chromatogram of 1 ml of infant serum with 300 pg ^{57}CoB$_{12}$. Bab M., go 17 days. Experiment number 11 in table 1

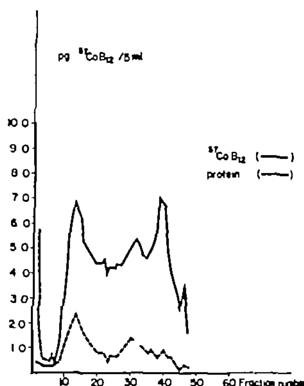


Fig 16. DEAE-cell lose chromatogram of 1 ml of infant serum with 300 pg CoB$_{12}$. Baby R., age 30 days. Experiment number 13 in t ble 1

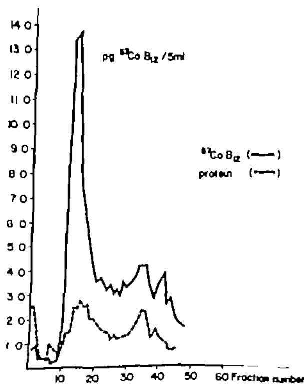


Fig 17 DEAE-cellulose hromatogram f 1 ml of inf nt serum ith 300 pg ^{57}CoB$_{12}$. Age 86 days. Experiment number ~~ in table 1

pg $^{57}Co\ B_{12}$ /5ml

$Co^{57}B_{12}$

PROTEIN

FRACTION NUMBER

Fig. 23. DEAE cellulose chromatogram of 50 ml of cord serum with 200 pg/ml $^{57}CoB_{12}$. The peak fractions for TC II, PTC and TC I are 40, 52 and 68, respectively.

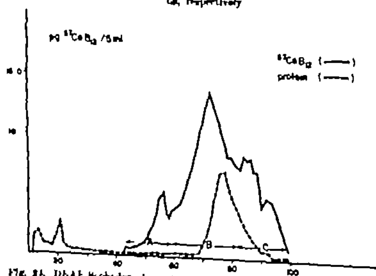


Fig. 24. DEAE Sephadex chromatogram of 10 ml of cord serum with 200 pg/ml $^{57}CoB_{12}$. The dimensions of the column were 2 × 11 cm.

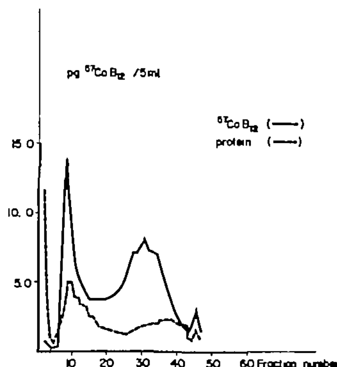


Fig 1 DEAE-cellulose chromatogram of 1 ml of serum from a deliveri g mother with 300 pg CoB$_{12}$. Experiment n mber 10 in table 1 is of the child of this mother

Characterization of the B_{12} binders in cord serum

DE 1E-chromatography on big columns

DE \E-chromatography on a big column was used as a starting procedure in the characterization of the individual binders. Figure 22 shows a chromatogram of 40 ml of normal adult serum with 125 pg of ^{57}CoB$_{12}$ added per 1 ml Eight lots of cord serum were processed in the same manner and the resulting chromatograms showed three activity peaks analogous to those described previously Figure 23 shows a chromatogram of 50 ml of cord serum with 300 pg of labeled B_{12} added per 1 ml

One lot of cord serum was processed using DEAE-Sephadex® instead of DEAE-cellulose. This chromatogram illustrated in figure 24 had a slightly different appearance but still contained the same components.

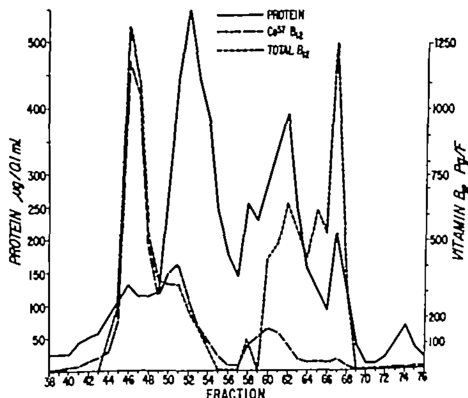


Fig 22. DEAE-cellulose hromatogram of 40 ml f normal adult serum with 125 pg/ml ^{57}CoB$_{12}$. Total B_{12} is the result of the *E glena gracilis* assay Fracti ns 1—37 did not co tain radioactivity and were ot illustrated. Th peak of TC II is in fraction 46, that f TC I in fraction 67

pg ^{57}Co B_{12} /5 ml

Co^{57}B$_{12}$

PROTEIN

FRACTION NUMBER

Fig. 23. DEAE-cellulose chromatogram of 50 ml of cord serum with 300 pg/ml ^{57}CoB$_{12}$. The peak fractions for TC II, FTC and TC I are 40, 53 and 68 respectively

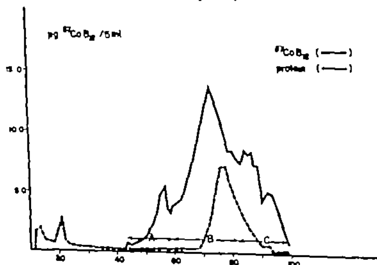


Fig. 24. DEAE Sephadex chromatogram of 10 ml of cord serum with 300 pg/ml ^{57}CoB$_{12}$. The dimensions of the column were 2 × 11 cm.

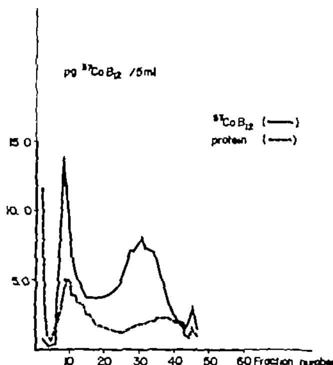


Fig 1. DEAE-cellulose chromatogram of 1 ml of serum from a delivering mother with 300 pg ^{57}CoB$_{12}$. Experiment number 10 in table 1 is of the child of this mother

Characterization of the B_{12} binders in cord serum

DEAE-chromatography on big columns

DEAE-chromatography on a big column was used as a starting procedure in the characterization of the individual binders. Figure 22 shows a chromatogram of 40 ml of normal adult serum with 125 pg of ^{57}CoB$_{12}$ added per 1 ml. Eight lots of cord serum were processed in the same manner and the resulting chromatograms showed three activity peaks analogous to those described previously. Figure 23 shows a chromatogram of 50 ml of cord serum with 300 pg of labeled B_{12} added per 1 ml.

One lot of cord serum was processed using DEAE-Sephadex® instead of DEAE-cellulose. This chromatogram illustrated in figure 24 had a slightly different appearance but still contained the same components.

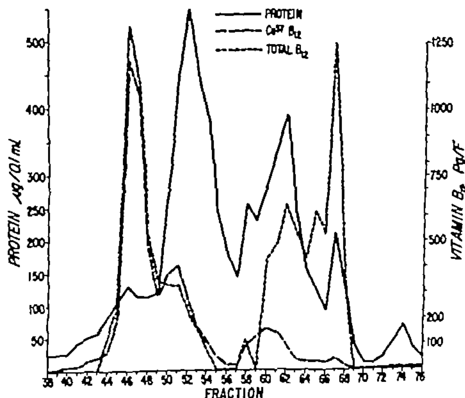


Fig 22. DEAE-cellulose chromatogram of 40 ml of normal adult serum with 125 pg/ml ^{57}CoB$_{12}$. Total B_{12} is the result of the *E gracilis* assay *Fractions* 1—37 did not contain radioactivity and were not illustrated. The peak of TC II is in fraction 46, that of TC I in fraction 68

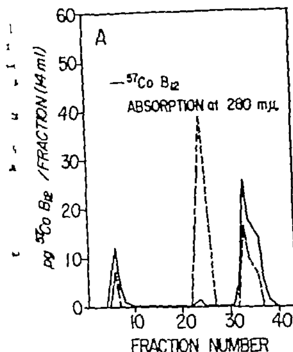


Fig 26. CM-cellulose chromatogram of the A-peak from the DEAE-cellulose chromatography illustrated in figure 23

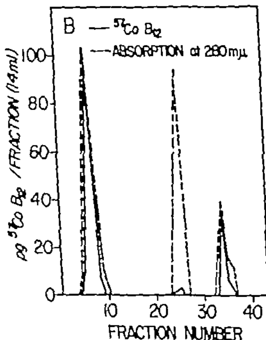


Fig 27 CM-cellulose chromatogram of the B-peak from the DEAE-cellulose chromatograph illustrated figure 23.

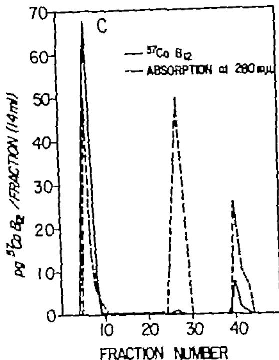


Fig 28. CM-cellulose chromatogram of the C-peak from the DEAE-cellulose chromatography illustrated in figure 23.

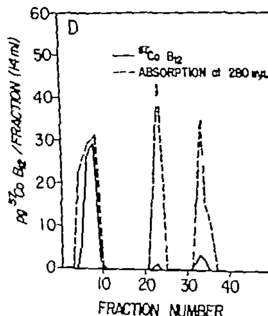


Fig. 29. CM-cellulose chromatogram of the D-peak from the DEAE-cellulose chromatography illustrated in figure 23.

CM-cellulose chromatography

The activity peaks from DEAE-chromatographies were ultrafiltered and dialyzed for chromatography on carboxymethyl cellulose columns. Figures 25 through 29 illustrate a DEAE-chromatogram with the subsequent CM-cellulose chromatograms of its different activity peaks.

The first DEAE peak (A) consisted mainly of material eluted from the CM-column by the final buffer. This material was called CM purified TC II and was used for the further characterization of the properties of TC II.

The second DEAE-peak (B) was mainly eluted from the CM-cellulose by the starting buffer. This non retaining material was called CM purified FTC. The retaining part of the B-peak, or that which was later eluted with the final buffer, can be considered to result from the contamination with the A peak.

The third DEAE peak as well as the last part of the chromatogram (C and D) still contained trace amounts of TC II like material. The main part of these peaks was non retaining i.e. eluted with the starting buffer and referred to as CM purified TC I.

The CM-chromatography did not separate FTC and TC I, but it did separate them from TC II and eliminate a large amount of the non B_{12} binding proteins.

When the radioactivity peaks from the DEAE-Sephadex run (figure 24) were processed by CM-chromatography, 55 %, 22 % and 48 % of the A, B- and C-peaks, respectively, were found to have the properties of TC II in CM-chromatography, that is they were retained until the final buffer. This spreading of TC II could already be seen in the low appearance of the A peak in the DEAE-Sephadex chromatogram.

Electrophoretic studies

The CM purified binders from five different DEAE-chromatographies were concentrated by ultrafiltration and dialyzed against the appropriate buffer prior to electrophoresis. Because of the differences in the properties of the gel and the possible differences in the electric current between the individual ex

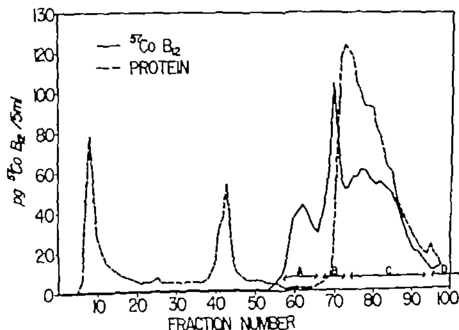


Fig 25. DEAE-cellulose chromatogram of 50 ml of cord serum with 300

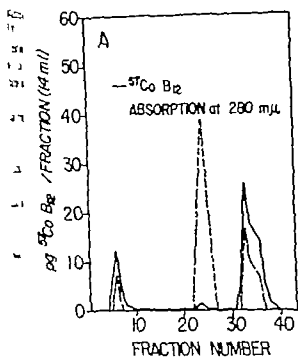


Fig. 26. CM-cellulose chromatogram of the A peak from the DEAE-cellulose chromatograph illustrated in figure 25

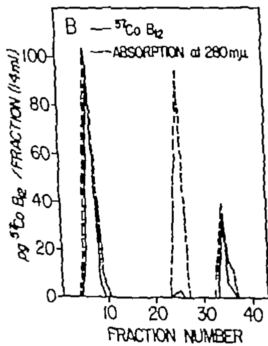


Fig. 27. CM-cellulose chromatogram of the B-peak from the DEAE-cellulose chromatography illustrated in figure 25

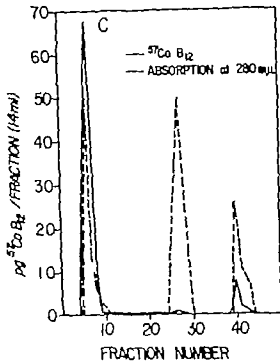


Fig. 28. CM-cellulose chromatogram of the C peak from the DEAE-cellulose chromatography illustrated in figure 25.

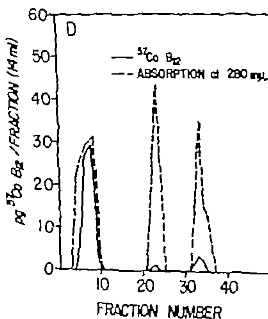


Fig. 29. CM-cellulose chromatogram of the D peak from the DEAE-cellulose chromatography illustrated in figure 25.

periments, the measured mobility of the same protein is not necessarily the same for each experiment. Thus no direct comparisons can be made between different *experiments*, only the mobilities of proteins run in parallel on the same block can be compared.

Electrophoresis at pH 8.6 Eleven experiments with two or three parallel samples were performed. Table 3 gives the mobilities for the different binders in these experiments. The mobility of TC II from cord serum was the same as the mobility of TC II from adult serum. FTC had a mobility between TC I and TC II. Figures 30 through 33 are selected to illustrate the electrophoretic behavior of the $^{57}CoB_{12}$-protein complexes. Figure 30 also includes the distribution of serum proteins in the geon block. TC I moved in the fast α-globulin region and TC II in the β-globulin region. FTC which had an intermediate mobility was thus found in the α-globulin region.

Electrophoresis at pH 4.5 Four electrophoretic experiments with three $^{57}CoB_{12}$ protein complexes in each were performed at pH 4.5 Table 4 gives the mobilities observed in these experiments. Figures 34 and 35

Table 3. *Electrophoresis at pH 8.6*

No	Binder	Mobility (cm)
1	FTC	+3
	TC II cord serum	+1
	TC II, adult serum	+1
2	TC II adult serum	+1
	FTC	+1
	TC I cord serum	+2
3	TC II adult serum	+4
	FTC	+4
	TC I cord serum	+7
4	TC II, adult serum	+4
	FTC	+5
5	TC II, adult serum	+3
	FTC	+4
	TC I, cord serum	+6
6	TC II, cord serum	+3
	FTC	+6
	TC I, cord serum	+8
7	TC II cord serum	+4
	FTC	+6
	TC I cord serum	+9
8	TC II, cord serum	+3
	FTC	+4
	TC I, cord serum	+3
9	TC II, adult serum	+
	FTC	+3
	TC I, cord serum	+5
10	TC II adult serum	+3
	FTC	+4
	TC II cord serum	+3
11	TC II adult serum	+3
	TC II, cord serum	+3
	TC I, cord serum	+6

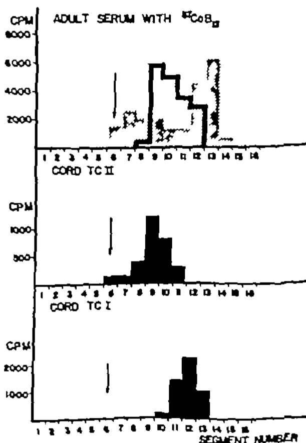


Fig. 30. Geon block electrophoresis at pH 8.6. The black columns represent radioactivity in the segments. The shaded columns represent the amount of protein eluted from the segments. The arrow points to the segment of application.

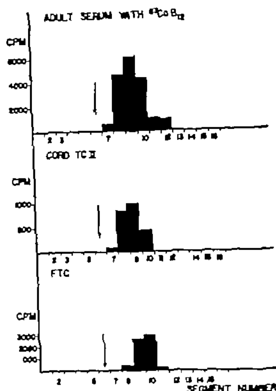


Fig. 31. Geon block electrophoresis at pH 8.6.

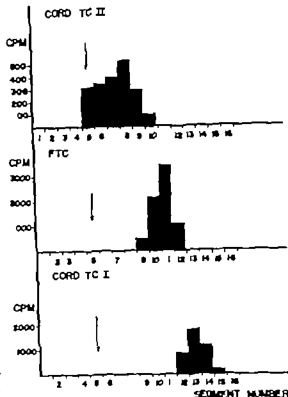


Fig. 32. Geon block electrophoresis at pH 8.6.

Fig. 33. Geon block electrophoresis at pH 8.6.

illustrate two of the experiments. TC II stayed at the point of application or had a slightly cathodal mobility and TC I had an anodal mobility. FTC had an anodal mobility which was somewhat less than that of TC I.

Table 4. *Electrophoresis at pH 4.5*

N	Binder	Mobility (cm)
12	FTC	+2
	TC II, cord serum	0
	TC II, adult serum	0
13	TC II, adult serum	−1
	FTC	+2
	TC I, cord serum	+3
14	TC II, cord serum	0
	FTC	+2
	TC I, cord serum	+3
15	TC II, cord serum	0
	FTC	+2
	TC I, cord serum	+4

periments, the measured mobility of the same protein is not necessarily the same for each experiment. Thus no direct comparisons can be made between different experiments, only the mobilities of proteins run in parallel on the same block can be compared.

Electrophoresis at pH 8.6 Eleven experiments with two or three parallel samples were performed. Table 3 gives the mobilities for the different binders in these experiments. The mobility of TC II from cord serum was the same as the mobility of TC II from adult serum. FTC had a mobility between TC I and TC II. Figures 30 through 33 are selected to illustrate the electrophoretic behavior of the $^{57}CoB_{12}$-protein complexes. Figure 30 also includes the distribution of serum proteins in the geon block. TC I moved in the fast α-globulin region and TC II in the β-globulin region. FTC which had an intermediate mobility was thus found in the α_2-globulin region.

Electrophoresis at pH 4.5 Four electrophoretic experiments with three CoB_{12} protein complexes in each were performed at pH 4.5. Table 4 gives the mobilities observed in these experiments. Figures 34 and 35

Table 3 *Electrophoresis at pH 8.6*

No	Binder	Mobility (cm)
1	FTC	+3
	TC II, cord serum	+1
	TC II, adult serum	+1
2	TC II, adult serum	+1
	FTC	+1
	TC I, cord serum	+3
3	TC II, adult serum	+4
	FTC	+4
	TC I, cord serum	+7
4	TC II, adult serum	+4
	FTC	+5
5	TC II, adult serum	+3
	FTC	+4
	TC I, cord serum	+6
6	TC II, cord serum	+3
	FTC	+6
	TC I, cord serum	+8
7	TC II, cord serum	+4
	FTC	+6
	TC I, cord serum	+9
8	TC II, cord serum	+3
	FTC	+4
	TC I, cord serum	+5
9	TC II, adult serum	+2
	FTC	+3
	TC I, cord serum	+5
10	TC II, adult serum	+3
	FTC	+4
	TC II, cord serum	+3
11	TC II, adult serum	+3
	TC II, cord serum	+3
	TC I, cord serum	+6

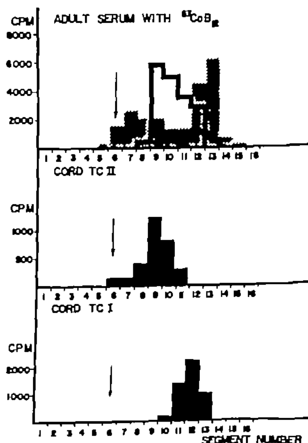


Fig. 30 Geon block electrophoresis at pH 8.6. The black columns represent radioactivity in the segments. The shaded columns represent the amount of protein eluted from the segments. The arrow points to the segment of application.

column was used to study the behavior of labeled whole serum on gel filtration.

Gel filtration of purified binders. CM purified binders from five different DEAE-chromatographies were studied. Table 5 summarizes the results. The molecular size of FTC was found to correspond to a molecular weight of 123,000. The molecular size of TC I did not differ from that of FTC.

Gel filtration of CoB labeled serum. Twelve experiments were performed using cord serum samples labeled with $^{57}CoB_{12}$. Seven different sera were studied and five of these with two amounts of labeled B_{12} added to them, 300 pg/ml and 2000 pg/ml. Two sera were studied only with 300 pg/ml. The experiments are listed in Table 6. The B binders were separated into two peaks. One was eluted before the albumin peak and thus consisted of material which had a molecular size larger than albumin. As shown above both FTC and TC I are included in this group. The other peak appeared after albumin as described for TC II by Hom et al (1966). Therefore the large binders (FTC and TC I) made up one peak and TC II the other as eluted from Sephadex G 100 columns. The average amount of added B bound to the large binders was 52.6 % with a range from 4 % to 89 %. The amount of added B had little influence on its distribution between the binders. No systematic study was performed on the distribution of added B_{12} in normal adult serum. Only three experiments were performed on adult material with 300 pg of CoB added per 1 ml. 16 %, 19 % and 15 % of the added B_{12} was bound to the large binders. Figure 36 illustrates one of the adult experiments and figure 37 the experiment number 3 on cord serum (300 pg/ml added).

The content of native B in the different binders

When the fractions from a DEAE-chromatogram of normal adult serum were assayed for their content of vitamin B, figure 22 resulted. Figure 38 is a differently constructed illustration of the same run

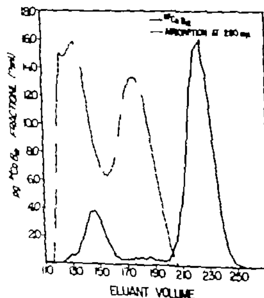


Fig. 36. Sephadex G 100 gel filtration of 1 ml of normal adult serum with 300 pg CoB. Eluant volume is expressed in ml.

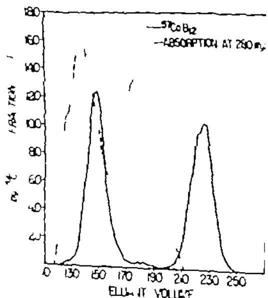


Fig. 37. Sephadex G-100 gel filtration of 1 ml of cord serum with 300 pg ^{57}CoB...

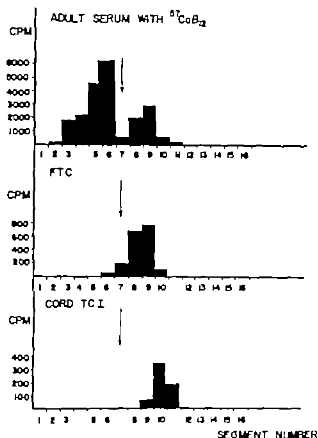


Fig 34 Geon block electrophoresis at pH 4.5

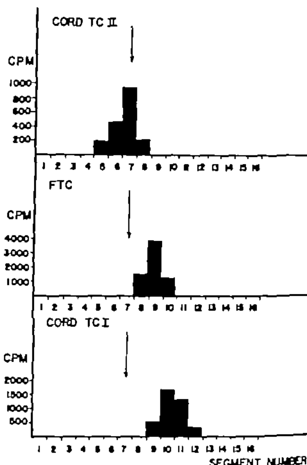


Fig 35. Geon block electrophoresis at pH 4.5.

Gel filtration on Sephadex® columns

Gel filtration on Sephadex was used for two purposes. Sephadex G 200 column was used to estimate the molecular sizes of the CM purified B binders, and Sephadex G 100

Table 5 *Molecular weight estimations by Sephadex G 200 gel filtration*

F T C	T C I
135 000	145,000
110 000	92,000
1[illegible]3 000	1[illegible]3 000
135,000	140 000
145 000	115,000
92,000	140 000
1[illegible]3,000	Range 92,000—145,000
125 000	Mean 1[illegible]0,000
Range 92,000—145,000	
Mean 123,000	

Table 6 *Sephadex G 100 gel filtration of CoB labeled cord serum*

No.	^{57}CoB$_{12}$ added pg/ml	% of radioactivity in TC II	% of radioactivity in large binders
1	300	[illegible]	50
	300	45	33
	2000	[illegible]	48
3	300	48	5
	[illegible]000		48
4	300	76	4
	[illegible]000	8	22
5	300		28
	[illegible]000	6	4
6	300	70	0
	[illegible]000	43	5
7	300	11	59

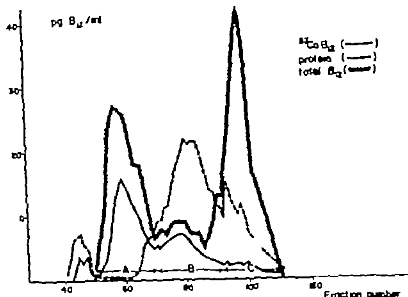


Fig. 40. DEAE-cellulose chromatogram of 20 ml of cord serum with 200 pg/ml $^{57}CoB_{12}$. Fractions 1—40 did not contain radioactivity and were omitted from the illustration.

10 pg, total B_{12} and $^{57}CoB_{12}$, respectively These figures are influenced by the incomplete separation on the DEAE-column.

The second DEAE-column was run using 11.6 ml of cord serum where 10 pg $^{57}CoB_{12}$/ml was added. Here the first radioactivity peak contained 2310 pg of B_{12}, the second 1950 pg, and the third 2445 pg as assayed by *Euglena*. The high amount of B_{12} in the second peak (FTC) was not in agreement with the results from the column described above Furthermore, the sum of the B_{12} values was 6705 pg, which makes the B_{12} concentration in the original sample 568 pg/ml. The serum was assayed in the same run and its B_{12} concentration was found to be 406 pg/ml. The B_{12} in the FTC-peak was mainly found in two fractions which gave high readings. These fractions were preceded, followed, and separated from each other by fractions containing little B_{12}. Thus, there is evidence that in this run the B_{12} content in FTC was an artefact, probably due to contamination.

The third DEAE-chromatography used 20 ml of cord serum with 300 pg radioactive B_{12} added per 1 ml. Figure 40 illustrates the results of this run. When the difference between total and added B_{12} for each peak was calculated, the A-peak (TC II) was found to contain 4295 pg of native B_{12}, the B-peak (FTC) 1211 pg, and the C-peak (TC I) 9681 pg. As can be seen from figure 40, part of the native B_{12} in the B-region was due to TC I.

Thus, these three DEAE-chromatograms show the presence of native B_{12} in the TC II fraction of cord serum besides the main location of it in TC I. They also indicate the absence of significant amounts of native B_{12} in FTC

The uptake of vitamin B_{12} by HeLa cells from different $^{57}CoB_{12}$-protein complexes

CM purified binders from five different cord serum DEAE-chromatographies were used. The data from the cell uptake experiments is presented in detail in Table 7 The same data grouped for each binder is presented in Table

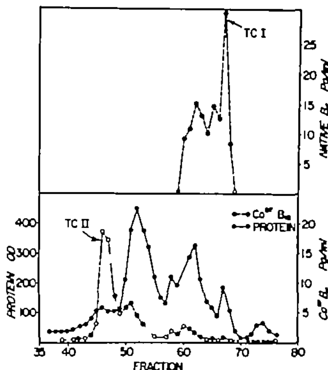


Fig 38. A reconstruction of figure 22 to demonstrate the difference in the location between native B_{12} and *in vitro* added $^{57}CoB_{12}$ in a DEAE-cellulose chromatogram of normal adult serum.

where 125 pg/ml labeled B_{12} was added to 40 ml of normal adult serum and the chromatography performed on a big DEAE column. Total B_{12} was measured by the *Euglena gracilis* assay In figure 38 the values for native B_{12} were obtained by subtracting the amount of radioactive B_{12} from the Euglena results. Native B was located at the end of the chromatogram, that is in TC I.

Three batches of cord serum were analyzed as described below

Figure 39 presents an illustration of 42 ml of cord serum processed and analyzed as above, with 10 pg of labeled B_{12} added per 1 ml of serum. Native B was found both in TC I and in TC II but the region of FTC where most of the added B_{12} was located was essentially free from native B_{12}. The different regions of this chromatogram were tested for their content of TC II by CM-cellulose chromatography In the A peak 69.5 % of the radioactivity was eluted from the CM-column by the final buffer The corresponding values for B C and D were 4 2 % 1.5 % and 9 0 % respectively The amounts of B_{12} in each fraction were A 6400 pg of which 37 pg was radioactive B 1372 pg and 106 pg C 1408 pg and 153 pg and D 7370 pg and

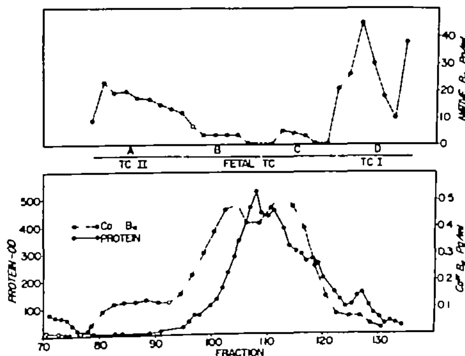


Fig 39 DEAE-cellulose chromatogram of 40 ml of cord serum with 10 pg/ml $^{57}CoB_{12}$. Fractions 1—70 were omitted from the illustration because they did not contain radioactivity

Table 7 cont.

Exp.	Binder	pg CoB$_{12}$ applied to the cells	Number of the cells 10^6	pg ^{57}CoB$_{12}$ taken up per million cells	% of total CoB$_{12}$ taken up
5	FTC	107.0	2.230	0	0
	FTC	109.9	2.400	0	0
	FTC	111.2	2.0[illegible]0	0	0
	TC I cord serum	74.6	2.000	0	0
	TC I, cord serum	74.5	3.100	0	0
	TC I, cord serum	71.6	2.150	0	0
	TC II, adult serum	131.9	3.100	1.93	4.5
	TC II adult serum	123.8	2.200	1.80	4.9
	B_{12} in saline	80.3	2.100	0.10	0.2[illegible]
	B_{12} in saline	78.8	3.200	0.09	0.26
6	TC II, cord serum	11.7	2.600	0.37	4.9
	TC II, cord serum	43.1	2.100	0.34	3.9
	TC II, cord serum	46.4	2.230	0.36	3.8
	TC II adult serum	103.1	2.100	1.41	4.[illegible]
	TC II, adult serum	107.0	2.830	1.49	5.1
	TC II, adult serum	119.[illegible]	2.[illegible]00	1.60	4.0
	B_{12} in saline	41.6	[illegible]8[illegible]0	0.03	0.25
	B_{12} in saline	42.9	2.400	0.03	0.33
7	TC II cord serum	43.9	[illegible]300	0.29	1.3
	TC II, cord serum	43.6	1.7[illegible]0	0.28	1.3
	TC II cord serum	29	2.030	0.22	1.3
	TC II, cord serum	29.2	1.300	0.20	1.3
	TC II adult serum	116.7	0.800	[illegible].44	1.7
	TC II adult serum	103.1	1.730	1.49	2.5
	B_{12} in saline	34.1	2.230	0.03	0.20
	B_{12} in saline	43.7	1.750	0.03	0.20
8	TC II cord serum	60.6	1.730	0.88	2.2
	TC II cord serum	60.4	1.900	1.32	3.6
	TC II cord serum	60.6	1.870	1.09	2.9
	TC II cord serum	60.2	2.000	1.11	3.2
	FTC	60.6	2.100	0.003	0.01
	FTC	60.9	2.100	0.01	0.04
	TC I cord serum	60.7	1.900	0.01	0.01
	B_{12} in saline	60.4	[illegible]1.0	0.03	0.16

Table 7 *Cell uptake experiments*

Exp.	Binder	pg $^{57}CoB_{12}$ applied to the cells	Number of the cells x 10^6	pg $^{57}CoB_{12}$ taken up per million cells	% of total CoB_{12} taken up
1	TC II cord serum	33.0	1 [illegible]00	0.[illegible]7	1 4
	TC II cord serum	33.0	1 690	0.20	1.3
	FTC	40 7	1 600	0	0
	FTC	40 7	1 760	0	0
	B_{12} in saline	2.8	1.930	0 01	0 [illegible] 0
2	TC II cord serum	[illegible]3.8	3.[illegible]30	0 61	2.8
	TC II cord serum	30.0	3.200	0.30	–
	TC II cord serum	35.6	[illegible]500	0.3[illegible]	—
	FTC	99.8	[illegible]930	0	0
	FTC	98.7	[illegible]300	0	0
	TC I cord serum	105 1	[illegible]700	0 06	0 14
	TC I cord serum	10[illegible]3	[illegible]900	0 06	0.1
	B_{12} in saline	88.0	3[illegible]0	0 17	0.63
3	TC II cord serum	31.8	0.930	0 4	1.3
	TC II cord serum	41 1	1.000	0.35	0.85
	FTC	93.8	1 100	0	0
	FTC	93.3	1 000	0	0
	TC I cord serum	69 6	1 100	0	0
	TC I cord serum	67.8	1.000	0	0
	TC II adult serum	1[illegible].8	0.800	[illegible]67	1 7
	TC II adult serum	116.0	0.930	[illegible]1	1.8
	B_{12} in saline	88.4	0.[illegible]00	0 17	0 13
	B_{12} in saline	82.9	1 000	0.1	0.14
	B_{12} in saline	49.3	1.030	0.04	0.07
	B_{12} in saline	48.0	1 030	0.03	0.07
4	TC II cord serum	30 6	3.600	0.33	3.3
	TC II cord serum	30.9	3.[illegible]30	0.3	3.3
	FTC	93.3	[illegible]930	0	0
	FTC	94.8	3 930	0	0
	TC I cord serum	69 0	3.600	0	0
	TC I cord serum	7[illegible]1	3.6[illegible]0	0	0
	TC II, adult serum	1[illegible]9.9	3.330	1 31	3.9
	TC II adult serum	128.8	3.330	1 6[illegible]	4.3
	B_{12} in saline	51.8	1 630	0 03	0 15
	B_{12} in saline	49.8	[illegible]000	0 06	0 31

Table cont.

Exp.	Blader	Pg $^{57}CoB_{12}$ pplied t the cells	Number f the cells 10^6	Pg CoB_{12} taken up per million cells	% f total $^{57}CoB_{12}$ taken p
					0
1.	FTC	107.0	2.2.0	0	0
	FTC	100.9	1.400	0	0
	FTC	111.2	3 030	0	0
	TC I, cord serum	4.6	2.000	0	0
	TC I, cord serum	74.8	2.100	0	0
	TC I cord serum	71.0	2.130	0	0
	TC II, adult serum	121.9	3 100	1.93	4.3
	TC II, adult serum	185.8	2.300	1.66	4.9
	B_{12} in saline	59.3	2.100	0.10	0.35
	B_{12} in saline	8.8	2.300	0 09	0.20
4.	TC II, cord serum	31.7	2.600	0.37	4.9
	TC II, cord serum	42.1	2.100	0.34	2.9
	TC II cord serum	48.4	2.2.0	0 .6	2.8
	TC II adult serum	103.4	2.100	1 41	4.2
	TC II adult serum	107.0	2.8.0	1 49	3.4
	TC II adult serum	119.2	3 300	1.60	4.9
	B_{12} in saline	41.0	2 8.0	0.03	0.33
	B_{12} in saline	43 9	3 400	0.03	0.33
	TC II cord serum	43 8	2.300	0.29	1.3
	TC II cord serum	43.5	1 730	0.25	1.3
	TC II, cord serum	59.2	2.0.0	0.22	1.3
	TC II, cord serum	59 2	1 300	0.30	1.2
	TC II adult serum	110.3	0 800	2.44	1.7
	TC II dult serum	103.1	1 730	1.49	2.3
	B_{12} in saline	34 1	2 250	0.03	0.20
	B_{12} in saline	43	1 750	0.03	0 20
8	TC II ord serum	60.6	1 750	0.96	2.2
	TC II cord serum	60 4	1.900	1.33	3.0
	TC II cord serum	60.6	1 6.0	1.09	2.9
	TC II cord serum	60.2	2 000	1.11	3.2
	FTC	60.6	.100	0.003	0.01
	FTC	60.9	2.100	0.01	0 04
	TC I, cord serum	60.7	1.900	0.01	0.01
	B_{12} in saline	60 4	.130	0.03	0.16

Table 8 *Cell uptake experiments*

Data for the uptake f CoB_{12} bound to d fferent proteins
The results are expressed as picograms per million cells.

TC II cord serum		TC II ad lt serum		FTC		TC I co d serum		$^{r}CoB_{12}$ in sal ne	
Applied	Taken up	Applied	Taken up	Applied	Taken up	Applied	Taken up	Applied	Taken up
19.4	0._7	159.8	.07	_3.4	0	75.9	0.06	1.4	0.01
19.5	0.26	12_	_1	23.3	0	35.4	0.00	7.1	0.17
2_.7	0.64	38.8	1 1	33.8	0	03_	0	1*0_	0.17
11.3	0.30	38.4	1.03	39.5	0	6 5	0	82.9	0.1
14._	0.3_	4_.5	1.93	88.1	0	19._	0	40.9	0.04
33.4	0.4	38.1	1.60	93.3	0	19.8	0	43.	0.03
41.1	0.35	*7.8	1.49	31.0	0	4.8	0	31.4	0.0
10._	0.33	34.1	1.60	4.0	0	4._	0	19._	0.06
0.8	0.3_	34.0	1.44	32.9	0	22.7	0	28.8	0.10
11.6	0.57	145.5	_44	32.4	0	36.0	0.01	4.6	0.09
14.1	0.54	00.1	1.49	36.3	0			14.6	0.05
14.0	0.56			33._	0.003			1_.9	0.05
19.1	0.29			33.3	0.01			*4.1	0.03
_3.0	0.38							*0.1	0.03
14.3	0.22							22.3	0.03
22.4	0.30								
29.8	0.56								
36.5	1.33								
37.6	1.09								
34.6	1.11								
Mean	0.5_	Mean	1.85	Mean:	0.001	Mean	0.01	Mean:	0.07
Range	0.2_—1.33	Range	1.44—_.07					Range	0.01—0.17

Table 9. *Summary of the HeLa cell uptake experiments*

Binder	Number of experiments	Uptake as pg of $^{57}CoB_{12}$ per million cells	
		Mean	Range
TC II, cord serum	20	0.52	0.22—1.33
TC II, adult serum	11	1.85	1.44—2.67
FTC	13	0.001	0—0.01
TC I, cord serum	10	0.01	0—0.04
B_{12} in saline	15	0.07	0.01—0.17

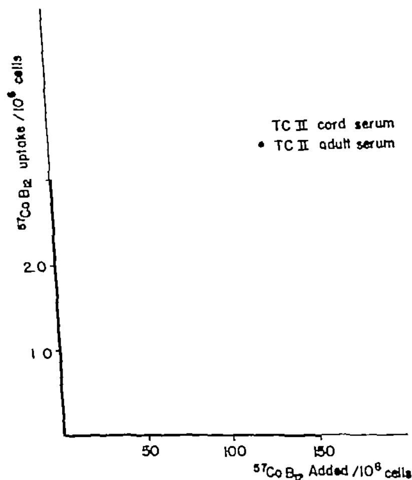


Fig. 41. HeLa cell uptake of $^{57}CoB_{12}$ from adult and cord serum TC II. The amount of CoB_{12} is expressed in picograms.

Table 8 *Cell uptake experiments*

Data for the uptake f $^{57}CoB_{12}$ bo nd to d fferent proteins
The results are expressed as picograms per million cells.

TC II cord serum		*TC II adult serum*		*FTC*		*TC I co d serum*		*$^{57}CoB_{12}$ in sal ne*	
Applied	Taken up	Applied	T ke up	Applied	Taken up	Applied	Taken up	Applied	Taken up
19.4	0.2_	139.8	_.67	_4	0	38.9	0.06	1.4	0.01
19.5	0.26	122.2	_.21	_3.3	0	33.4	0.06	1	0.17
22.7	0.64	38.8	1.31	33.8	0	03_	0	1_.6_	0.1
11.3	0.30	38.4	1.65	39.5	0	07.8	0	8_.9	0.12
14._	0.3_	42.5	1.93	89.1	0	19._	0	40.9	0.04
33.4	0.42	38.1	1.56	93.3	0	19.8	0	45.7	0.03
41.1	0.33	_7.8	1.49	31.6	0	4.8	0	31.4	0.03
10._	0.33	31.1	1.66	24.0	0	4_	0	19._	0.00
9.8	0.32	34.0	1.44	3_.9	0	22.7	0	28.8	0.10
11.6	0.57	14_._	_.44	32.4	0	36.6	0.01	4.6	0.00
14.1	0.54	60.1	1.49	36.5	0			14.6	0.05
14.9	0.36			33._	0.003			1_.9	0.03
19.1	0.29			33.3	0.01			41	0.03
23.0	0.38							_0.1	0.03
14.3	0.2_							32.3	0.03
22.4	0.30								
39.8	0.80								
36.5	1.33								
37.0	1.09								
34.6	1.11								
Mean	0.52	Mean	1.83	Mea :	0.001	Mean	0.01	Mean	0.07
Range	0.22—1.33	Ra ge	1.44—_.67					Range	0.01—0.1

Table 9 *Summary of the HeLa cell uptake experiments*

Binder	Number of experiments	Uptake as pg of $^{57}CoB_{12}$ per million cells	
		Mean	Range
TC II, cord serum	20	0.92	0.23—1.33
TC II, adult serum	11	1.83	1.44—2.67
FTC	13	0.001	0—0.01
TC I, cord serum	10	0.01	0—0.06
B_{12} in saline	15	0.07	0.01—0.17

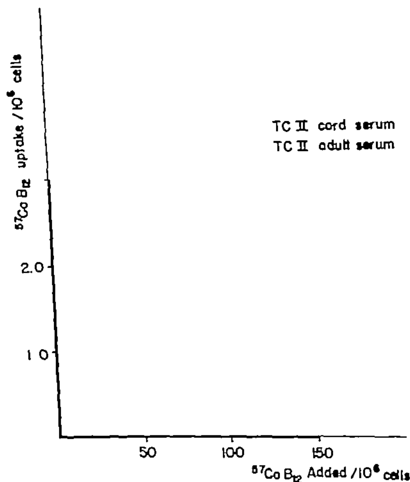


Fig. 41. HeLa cell uptake of $^{57}CoB_{12}$ from adult and cord serum TC II. The amount of CoB_{12} is expressed in picograms.

8 Table 9 gives the summary for the experiments. There was little uptake from the B_{12}-saline solution without any binders. B_{12} from complexes with FTC and TC I was only occasionally taken up and even then to an insignificant degree. TC II promoted the uptake. There was a difference between the uptake of $^{57}CoB_{12}$ from adult and cord serum TC II. Since never more than 5.4 % of the total applied labeled B_{12} was taken up, there was always an excess of the vitamin available to the cells. It is still possible that the amount taken up was influenced by the amount given to the cells. To study this possibility, figure 41 was constructed. It gives a suggestion that this kind of phenomenon did exist, while it also shows that even at the same level of $^{57}CoB_{12}$ applied to the cells, more of it was taken up from adult TC II than from cord serum TC II. However, the actual phenomenon is the uptake of vitamin B_{12}, and not that of ^{57}Co-labeled B_{12}. As shown in the previous section, the amount of native B_{12} in cord serum TC II was different from that in adult TC II. The lesser uptake of $^{57}CoB_{12}$ from cord serum TC II is at least partly due to the dilution by cold endogenous B_{12}. The concentrations of native B_{12} in the fractions studied were not measured. Thus no exact comparisons can be made between adult and cord serum TC II as to the uptake of B_{12} from them.

Discussion

The binding of added B_{12} in normal adult serum

The purpose of the present work was not to make a systematic study of the phenomenon of B_{12} binding in normal adult serum. Such studies using the same methods as presented here have been published (Hall and Finkler 1965, 1966a, Hom and Olesen 1967). In this study adult samples served as a comparison for the cord serum binding pattern and as a check for the chromatographic and other techniques employed. The finding that most of the added B_{12} in normal adult serum was bound to TC II is in good agreement with the results by Hall and Finkler (1965, 1966a). The binding in some sera of added B_{12} with proteins eluted from the DEAE-column in between TC II and TC I has also been reported earlier (Hall and Finkler 1966a). This binding was thought to be nonspecific and was not explored further. This assumed nonspecificity and irrelevance to vitamin B_{12} metabolism may be correct, but it is not necessarily so. The binding with these proteins when subsaturation amounts of B_{12} were added may be a different phenomenon from the overflow binding found in all sera when large amounts of B_{12} were added. No systematic study on the occurrence of this type of binding has been performed earlier, nor was it performed in the present work. The properties of this B_{12}-protein complex, other than its behavior in DEAE-chromatography, have not been studied. This middle binder in normal adult serum will be referred to as the FTC-like binder. While there is no reason to assume that this binder might be of great importance in the metabolism of vitamin B_{12}, it becomes interesting when one starts comparing adult and newborn binding systems.

The work by Hom and Ahluwalia (1968) provokes further discussion concerning the possible occurrence of more than two B_{12} binders in normal adult serum. Using gel filtration on Sephadex G 200 columns, they found three binders. The third binder possessing a large molecular size, they designated TC 0. Whether it has any correlation to the FTC like binder remains to be seen. If one assumes, that the FTC like binder has the same molecular size as FTC, it would be included in the TC I peak as eluted from gel filtration. This would partly explain the wide range of binding capacity attributed to TC I in the study by Hom and Ahluwalia.

The binding of added B_{12} in cord serum

The B_{12}-binding pattern in cord serum as studied by the "mini-column technique" of DEAE-chromatography is different from the adult system. This can be seen in the binding of added B_{12} to a protein, so called fetal transcobalamin (FTC) in the middle region of the chromatogram. *Binding to FTC was a constant finding* in the studied samples of cord serum and it occurred regardless of the amount of added B_{12}. The experiments with small amounts of added B_{12} demonstrate the difference between this phenomenon and the secondary binding to plasma proteins other than TC II and TC I after the saturation of these primary binders (Hall and Finkler 1966a). The four experiments with 1000 pg of B_{12} added per 1 ml of serum suggest that although the binding avidity of FTC is strong,

8 Table 9 gives the summary for the experiments. There was little uptake from the B_{12}-saline solution without any binders. B_{12} *from* complexes with FTC and TC I was only occasionally taken up and even then to an insignificant degree TC II promoted the uptake There was a difference between the uptake of $^{57}CoB_{12}$ from adult and cord serum TC II Since never more than 5.4 % of the total applied labeled B_{12} was taken up there was always an excess *of the vitamin available* to the cells. It is still possible that the amount taken up was influenced by the amount given to the cells. To study this possibility figure 41 was constructed It gives a suggestion that this kind of phenomenon did exist while it also shows that even at the same level of $^{57}CoB_{12}$ applied to the cells, more of it was *taken up from adult TC II than from cord* serum TC II However the actual phenomenon is the uptake of vitamin B_{12}, and not that of ^{57}Co-labeled B_{12} As shown in the previous section the amount of native B_{12} in cord serum TC II was different from that in adult TC II The lesser uptake of $^{57}CoB_{12}$ from cord serum TC II is at least partly due *to the dilution by "cold" endogenous* B_{12} The concentrations of native B_{12} in the fractions studied were not measured. Thus no exact comparisons can be made between adult and cord serum TC II as to the uptake of B_{12} from them

this FTC-like binder at the time of delivery would elucidate this. Perhaps a correlation between B_{12} binding to FTC and some parameter of feto-maternal hemorrhage could be demonstrated. The presence of fetal hemoglobin in maternal circulation could be used for this purpose. Primarily of interest is the elucidation of the properties of the FTC-like binder to learn whether it is FTC or not.

As to the correlation of the binding to FTC in maternal blood with the degree of binding to FTC in the blood of the child of that mother the present material is too small to warrant any conclusions. It is, however interesting to note that in the case of slight binding to FTC at the age of 10 days (experiment number 7 in Table 1) the mother had a normal adult B_{12} binding pattern, identical to that illustrated in figure 19

Characterization of the B_{12} binders in cord serum

In DEAE-chromatograms of cord serum a binder corresponding to TC I was found. Further characterization if it by the methods used failed to detect any differences between it and adult TC I. It was shown to be the carrier of native B_{12} and to bind little of the added B_{12}. It behaved the same as adult TC I in the CM-cellulose chromatography system. Its electrophoretic mobility was in the fast globulin region and it had a molecular size corresponding to a molecular weight of about 120,000. It did not deliver its bound-B_{12} to HeLa cells. All the above features are the same as those described for adult TC I (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom and Olesen 1967)

A binder corresponding to TC II was also found in cord serum. It had the same behavior in the CM-cellulose chromatography system, and it had the same electrophoretic β mobility as adult TC II. It had a molecular size which was smaller than that of albumin. It caused a considerable uptake of B_{12} by HeLa cells, when the vitamin was introduced to the cells bound to it. The main difference between this binder and adult TC II was the content of native B_{12} in cord serum TC II. This phenomenon has not been described earlier for adult TC II (Hall and Finkler 1965, Gabuzda *et al.* 1965). However a personal communication with Hall (1967) after the completion of the present experiments has given supporting evidence for the possible occurrence of native B_{12} in TC II in some samples of adult serum. Further studies on this are underway. Thus the difference between adult and cord serum TC II may be more quantitative than qualitative. *The occurrence of* native B_{12} in cord serum TC II also explains the other found difference, the decreased uptake of $^{57}CoB_{12}$ by HeLa cells from cord serum TC II as compared to adult TC II.

The finding that TC II may contain native B_{12} contrary to the earlier concept is by no means revolutionary when considering its function. TC II is known to bind newly introduced B_{12} both *in vivo* and *in vitro* and further deliver it to the cells and tissues (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom 1967b, Retief *et al.* 1967b). If the balance between taking up B_{12} and delivering it to the tissues is in favor of the former, B_{12} will no doubt accumulate in TC II. It is not known whether it is an increased uptake or decreased delivering of B_{12} which makes cord serum TC II contain native B_{12}. Some difference in TC II itself is not excluded, but nothing in the present study favors such a concept.

The "new" B_{12} binder, the so called *fetal* transcobalamin, has no adult counterpart to compare it with. A similar binder was found, to a lesser degree and inconsistently in DEAE-chromatograms of adult serum, but it has not been characterized *further*. It may be the same binder and can be called the FTC-like binder. In the present study the basic difference between FTC and the other

its capacity is limited. The present data does not answer the question of whether the difference between adult and cord serum binding patterns is qualitative or quantitative, i.e. whether FTC is the same as the FTC-like binder in the chromatograms of some adult sera

The binding of added B_{12} in infant serum

In order to obtain information about the origin and disappearance of FTC infants of different ages were studied. There was a tendency towards less binding of added B_{12} to FTC in older infants, but the changing pattern was far from clear-cut. If FTC had its origin outside the infant, that is in the placenta or in the mother it would disappear at the same rate in each infant, depending on the turnover of the protein molecule. The inconsistent rate of disappearance indicates that FTC has its origin in the infant itself It remains to be explained, why in one infant at the age of 10 days an adult binding pattern exists, and in another at the age of 106 days a considerable amount of the added B_{12} is bound to FTC The possible factors which could have an influence on this phenomenon are the B_{12} concentration in the serum and the amount of it bound to TC II i.e. the saturation of the other binders. These things were not studied in the present work. Also to be considered is the fact, that even in normal adult serum there are differences as to the amount of added B_{12} bound to an FTC-like binder The factors influencing this phenomenon are equally unexplained

To study serial successive samples from the same infants is very informative in solving the problem of changing B_{12} binding pattern Obtaining this kind of material is naturally difficult, and the limited material presented here should be reviewed in this light. No definitive information concerning the disappearance of FTC could be obtained from this material It does suggest that binding to FTC diminishes during the first few weeks of life. This could very well reflect the gradual disappearance of FTC from the serum, although the amount of added B_{12} being bound to FTC does not necessarily parallel the concentration of FTC Various factors, such as the saturation of other B_{12} binders, may play a role in the distribution of added B_{12} between the binders. Adding labeled B_{12} is, however the only approach to FTC since there are no means of measuring its actual concentration.

In all the studied samples which were either cord serum or serum drawn from infants during the first week of life FTC occurred as one of the principal binders of added B_{12}, and the binding pattern was distinctly different from the adult binding pattern.

The binding of added B_{12} in maternal serum

The analyzed maternal serum samples did not give a clear-cut answer to the question concerning the existence or non-existence of FTC in the delivering mother Three of the samples were definitely of the adult type and five more could fit the adult pattern with some binding of added B_{12} to an FTC-like binder However four of the samples remained in the category of "abnormal binding to an FTC like binder

One possible explanation for the occurrence of FTC in the maternal circulation is that FTC is of fetal origin and may be carried over to the maternal side by a feto-maternal hemorrhage which is known to be a relatively common phenomenon (Cohen *et al* 1964) Such a hemorrhage is usually of a minor degree and thus the amount of FTC entering the maternal circulation would be very small. It could, however play a detectable role in the binding of added B_{12} if one assumes that the binding avidity of FTC for B_{12} is strong A study of serial samples from mothers with

this FTC-like binder at the time of delivery would elucidate this. Perhaps a correlation between B_{12} binding to FTC and some parameter of feto-maternal hemorrhage could be demonstrated. The presence of fetal hemoglobin in maternal circulation could be used for this purpose. Primarily of interest is the elucidation of the properties of the FTC-like binder to learn whether it is FTC or not.

As to the correlation of the binding to FTC in maternal blood with the degree of binding to FTC in the blood of the child of that mother the present material is too small to warrant any conclusions. It is, however interesting to note that in the case of slight binding to FTC at the age of 10 days (experiment number 7 in Table 1) the mother had a normal adult B_{12} binding pattern, identical to that illustrated in figure 10

Characterization of the B_{12} binders in cord serum

In DEAE-chromatograms of cord serum a binder corresponding to TC I was found. Further characterization of it by the methods used failed to detect any differences between it and adult TC I. It was shown to be the carrier of native B_{12} and to bind little of the added B_{12}. It behaved the same as adult TC I in the CM-cellulose chromatography system. Its electrophoretic mobility was in the fast α-globulin region and it had a molecular size corresponding to a molecular weight of about 120,000. It did not deliver its bound-B_{12} to HeLa cells. All the above features are the same as those described for adult TC I (Hall and Finkler 1965 1966a, Finkler and Hall 1967 Hom and Olesen 1967)

A binder corresponding to TC II was also found in cord serum It had the same behavior in the CM-cellulose chromatography system, and it had the same electrophoretic β mobility as adult TC II It had a molecular size which was smaller than that of albumin. It caused a considerable uptake of B_{12} by HeLa cells, when the vitamin was introduced to the cells bound to it. The main difference between this binder and adult TC II was the content of native B_{12} in cord serum TC II This phenomenon has not been described earlier for adult TC II (Hall and Finkler 1965 Gabuzda *et al.* 1965) However a personal communication with Hall (1967) after the completion of the present experiments has given supporting evidence for the possible occurrence of native B_{12} in TC II in some samples of adult serum. Further studies on this are underway Thus the difference between adult and cord serum TC II may be more quantitative than qualitative. The occurrence of native B_{12} in cord serum TC II also explains the other found difference the decreased uptake of $^{57}CoB_{12}$ by HeLa cells from cord serum TC II as compared to adult TC II.

The finding that TC II may contain native B_{12} contrary to the earlier concept is by no means revolutionary when considering its function. TC II is known to bind newly introduced B_{12} both *in vivo* and *in vitro* and further deliver it to the cells and tissues (Hall and Finkler 1965 1966a, Finkler and Hall 1967 Hom 1967b Retief *et al.* 1967b) If the balance between taking up B_{12} and delivering it to the tissues is in favor of the former B_{12} will no doubt accumulate in TC II. It is not known whether it is an increased uptake or decreased delivering of B_{12} which makes cord serum TC II contain native B_{12}. Some difference in TC II *itself is not excluded*, but nothing in the present study favors such a concept.

The "new" B_{12} binder the so called fetal transcobalamin, has no adult counterpart to compare it with. A similar binder was found, to a lesser degree and inconsistently in DEAE-chromatograms of adult serum, but it has not been characterized further It may be the same binder and can be called the FTC-like binder In the present study the basic difference between FTC and the other

its capacity is limited. The present data does not answer the question of whether the difference between adult and cord serum binding patterns is qualitative or quantitative i.e whether FTC is the same as the FTC-like binder in the chromatograms of some adult sera.

The binding of added B in infant serum

In order to obtain information about the origin and disappearance of FTC infants of different ages were studied. There was a tendency towards less binding of added B_{12} to FTC in older infants, but the changing pattern was far from clear-cut. If FTC had its origin outside the infant that is in the placenta or in the mother it would disappear at the same rate in each infant, depending on the turnover of the protein molecule. The inconsistent rate of disappearance indicates that FTC has its origin in the infant itself. It remains to be explained why in one infant at the age of 10 days an adult binding pattern exists, and in another at the age of 106 days a considerable amount of the added B is bound to FTC. The possible factors which could have an influence on this phenomenon are the B concentration in the serum and the amount of it bound to TC II i.e. the saturation of the other binders. These things were not studied in the present work. Also to be considered is the fact, that even in normal adult serum there are differences as to the amount of added B_{12} bound to an FTC-like binder. The factors influencing this phenomenon are equally unexplained.

To study serial successive samples from the same infants is very informative in solving the problem of changing B binding pattern. Obtaining this kind of material is naturally difficult, and the limited material presented here should be reviewed in this light. No definitive information concerning the disappearance of FTC could be obtained from this material. It does suggest that binding to FTC diminishes during the first few weeks of life. This could very well reflect the gradual disappearance of FTC from the serum, although the amount of added B , being bound to FTC does not necessarily parallel the concentration of FTC. Various factors, such as the saturation of other B_{12} binders, may play a role in the distribution of added B_{12} between the binders. Adding labeled B_{12} is, however, the only approach to FTC since there are no means of measuring its actual concentration.

In all the studied samples which were either cord serum or serum drawn from infants during the first week of life FTC occurred as one of the principal binders of added B_{12}, and the binding pattern was distinctly different from the adult binding pattern.

The binding of added B in maternal serum

The analyzed maternal serum samples did not give a clear-cut answer to the question concerning the existence or non-existence of FTC in the delivering mother. Three of the samples were definitely of the adult type and five more could fit the adult pattern with some binding of added B_{12} to an FTC-like binder. However, four of the samples remained in the category of "abnormal" binding to an FTC-like binder.

One possible explanation for the occurrence of FTC in the maternal circulation is that FTC is of fetal origin and may be carried over to the maternal side by a feto-maternal hemorrhage which is known to be a relatively common phenomenon (Cohen *et al* 1964). Such a hemorrhage is usually of a minor degree and thus the amount of FTC entering the maternal circulation would be very small. It could, however, play a detectable role in the binding of added B , if one assumes that the binding avidity of FTC for B_{12} is strong. A study of serial samples from mothers with

this FTC-like binder at the time of delivery would elucidate this. Perhaps a correlation between B_{12} binding to FTC and some parameter of feto-maternal hemorrhage could be demonstrated. The presence of fetal hemoglobin in maternal circulation could be used for this purpose. Primarily of interest is the elucidation of the properties of the FTC-like binder to learn whether it is FTC or not.

As to the correlation of the binding to FTC in maternal blood with the degree of binding to FTC in the blood of the child of that mother the present material is too small to warrant any conclusions. It is, however, interesting to note that in the case of slight binding to FTC at the age of 10 days (experiment number 7 in Table 1) the mother had a normal adult B_{12} binding pattern, identical to that illustrated in figure 19.

Characterization of the B_{12} binders in cord serum

In DEAE-chromatograms of cord serum a binder corresponding to TC I was found. Further characterization of it by the methods used failed to detect any differences between it and adult TC I. It was shown to be the carrier of native B_{12} and to bind little of the added B_{12}. It behaved the same as adult TC I in the CM-cellulose chromatography system. Its electrophoretic mobility was in the fast α-globulin region and it had a molecular size corresponding to a molecular weight of about 120 000. It did not deliver its bound B_{12} to HeLa cells. All the above features are the same as those described for adult TC I (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom and Olesen 1967).

A binder corresponding to TC II was also found in cord serum. It had the same behavior in the CM-cellulose chromatography system, and it had the same electrophoretic β mobility as adult TC II. It had a molecular size which was smaller than that of albumin. It caused a considerable uptake of B_{12} by HeLa cells, when the vitamin was introduced to the cells bound to it. The main difference between this binder and adult TC II was the content of native B_{12} in cord serum TC II. This phenomenon has not been described earlier for adult TC II (Hall and Finkler 1965, Gabuzda et al. 1965). However, a personal communication with Hall (1967) after the completion of the present experiments has given supporting evidence for the possible occurrence of native B_{12} in TC II in some samples of adult serum. Further studies on this are underway. Thus the difference between adult and cord serum TC II may be more quantitative than qualitative. The occurrence of native B_{12} in cord serum TC II also explains the other found difference: the decreased uptake of B_{12} by HeLa cells from cord serum TC II as compared to adult TC II.

The finding that TC II may contain native B_{12} contrary to the earlier concept is by no means revolutionary when considering its function. TC II is known to bind newly introduced B_{12} both in vivo and in vitro and further deliver it to the cells and tissues (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom 1967b, Retief et al. 1967b). If the balance between taking up B_{12} and delivering it to the tissues is in favor of the former, B_{12} will no doubt accumulate in TC II. It is not known whether it is an increased uptake or decreased delivering of B_{12} which makes cord serum TC II contain native B_{12}. Some difference in TC II itself is not excluded, but nothing in the present study favors such a concept.

The "new" B_{12} binder, the so called fetal transcobalamin, has no adult counterpart to compare it with. A similar binder was found, to a lesser degree and inconsistently, in DEAE-chromatograms of adult serum, but it has not been characterized further. It may be the same binder and can be called the FTC-like binder. In the present study the basic difference between FTC and the other

its capacity is limited. The present data does not answer the question of whether the difference between adult and cord serum binding patterns is qualitative or quantitative, i.e. whether FTC is the same as the FTC-like binder in the chromatograms of some adult sera.

The binding of added B_{12} in infant serum

In order to obtain information about the origin and disappearance of FTC infants of different ages were studied. There was a tendency towards less binding of added B_{12} to FTC in older infants, but the changing pattern was far from clear-cut If FTC had its origin outside the infant that is in the placenta or in the mother it would disappear at the same rate in each infant, depending on the turnover of the protein molecule. The inconsistent rate of disappearance indicates that FTC has its origin in the infant itself It remains to be explained why in one infant at the age of 10 days an adult binding pattern exists, and in another at the age of 106 days a considerable amount of the added B is bound to FTC The possible factors which could have an influence on this phenomenon are the B concentration in the serum and the amount of it bound to TC II i.e. the saturation of the other binders. These things were not studied in the present work. Also to be considered is the fact, that even in normal adult serum there are differences as to the amount of added B , bound to an FTC-like binder The factors influencing this phenomenon are equally unexplained

To study serial successive samples from the same infants is very informative in solving the problem of changing B binding pattern Obtaining this kind of material is naturally difficult, and the limited material presented here should be reviewed in this light. No definitive information concerning the disappearance of FTC could be obtained from this material. It does suggest that binding to FTC diminishes during the first few weeks of life. This could very well reflect the gradual disappearance of FTC from the serum, although the amount of added B_{12} being bound to FTC does not necessarily parallel the concentration of FTC Various factors, such as the saturation of other B_{12} binders, may play a role in the distribution of added B_1 between the binders. Adding labeled B_{12} is, however the only approach to FTC since there are no means of measuring its actual concentration

In all the studied samples which were either cord serum or serum drawn from infants during the first week of life FTC occurred as one of the principal binders of added B_{12}, and the binding pattern was distinctly different from the adult binding pattern

The binding of added B , in maternal serum

The analyzed maternal serum samples did not give a clear-cut answer to the question concerning the existence or non-existence of FTC in the delivering mother Three of the samples were definitely of the adult type and five more could fit the adult pattern with some binding of added B to an FTC-like binder However four of the samples remained in the category of abnormal binding to an FTC-like binder

One possible explanation for the occurrence of FTC in the maternal circulation is that FTC is of fetal origin and may be carried over to the maternal side by a feto-maternal hemorrhage which is known to be a relatively common phenomenon (Cohen *et al* 1964) Such a hemorrhage is usually of a minor degree and thus the amount of FTC entering the maternal circulation would be very small It could, however play a detectable role in the binding of added B ,, if one assumes that the binding avidity of FTC for B is strong A study of serial samples from mothers with

this FTC-like binder at the time of delivery would elucidate this. Perhaps a correlation between B_{12} binding to FTC and some parameter of feto-maternal hemorrhage could be demonstrated. The presence of fetal hemoglobin in maternal circulation could be used for this purpose. Primarily of interest is the elucidation of the properties of the FTC-like binder to learn whether it is FTC or not.

As to the correlation of the binding to FTC in maternal blood with the degree of binding to FTC in the blood of the child of that mother the present material is too small to warrant any conclusions. It is, however, interesting to note that in the case of slight binding to FTC at the age of 10 days (experiment number 7 in Table 1) the mother had a normal adult B_{12} binding pattern, identical to that illustrated in figure 19.

Characterization of the B_{12} binders in cord serum

In DEAE-chromatograms of cord serum a binder corresponding to TC I was found. Further characterization of it by the methods used failed to detect any differences between it and adult TC I. It was shown to be the carrier of native B_{12} and to bind little of the added B_{12}. It behaved the same as adult TC I in the CM-cellulose chromatography system. Its electrophoretic mobility was in the fast α-globulin region and it had a molecular size corresponding to a molecular weight of about 120,000. It did not deliver its bound B_{12} to HeLa cells. All the above features are the same as those described for adult TC I (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom and Olesen 1967).

A binder corresponding to TC II was also found in cord serum. It had the same behavior in the CM-cellulose chromatography system and it had the same electrophoretic β mobility as adult TC II. It had a molecular size which was smaller than that of albumin. It caused a considerable uptake of B_{12} by HeLa cells, when the vitamin was introduced to the cells bound to it. The main difference between this binder and adult TC II was the content of native B_{12} in cord serum TC II. This phenomenon has not been described earlier for adult TC II (Hall and Finkler 1965, Gabuzda et al. 1965). However a personal communication with Hall (1967) after the completion of the present experiments has given supporting evidence for the possible occurrence of native B_{12} in TC II in some samples of adult serum. Further studies on this are underway. Thus the difference between adult and cord serum TC II may be more quantitative than qualitative. The occurrence of native B_{12} in cord serum TC II also explains the other found difference: the decreased uptake of ^{57}Co B_{12} by HeLa cells from cord serum TC II as compared to adult TC II.

The finding that TC II may contain native B_{12} contrary to the earlier concept is by no means revolutionary when considering its function. TC II is known to bind newly introduced B_{12} both in vivo and in vitro and further deliver it to the cells and tissues (Hall and Finkler 1965, 1966a, Finkler and Hall 1967, Hom 1967b, Retief et al. 1967b). If the balance between taking up B_{12} and delivering it to the tissues is in favor of the former, B_{12} will no doubt accumulate in TC II. It is not known whether it is an increased uptake or decreased delivering of B_{12} which makes cord serum TC II contain native B_{12}. Some difference in TC II itself is not excluded, but nothing in the present study favors such a concept.

The new B_{12} binder, the so called fetal transcobalamin, has no adult counterpart to compare it with. A similar binder was found, to a lesser degree and inconsistently, in DEAE-chromatograms of adult serum, but it has not been characterized further. It may be the same binder and can be called the FTC-like binder. In the present study the basic difference between FTC and the other

binders, TC I and TC II is its different behavior in DEAE-cellulose chromatography. This can be explained by the differences in the electric charge of the molecules. These same differences are further reflected by electrophoretic mobilities. FTC has an intermediate mobility when compared with TC I and TC II and a mobility similar to α globulins when compared with serum proteins. In the CM-cellulose chromatography system used FTC behaved like TC I and was eluted from the column by the starting buffer. As to the molecular size it was similar to that of TC I, i.e. its molecular weight is approximately 120 000. FTC thus forms one peak with TC I when labeled serum is fractionated by gel filtration in Sephadex columns. When CoB_{12} bound to FTC was incubated with HeLa cells, there was no uptake by the cells. In this respect too, FTC behaves like TC I. The main difference between TC I and FTC besides the differences in the electric charge is the non-content of native B_{12} in FTC.

Finkler *et al.* (1968) showed that FTC reacts with an antiserum produced against TC I from leukemic blood and with an antiserum against the salivary "R-binder" but not with an antiserum against TC II. FTC thus seems to be immunologically similar to TC I and to belong to the "R-group" of B_{12} binders, which includes TC I and B binders in gastric juice, saliva, bile, cerebrospinal fluid and blood cells (Simons 1964, Stenman *et al.* 1967, Grasbeck 1967). Immunological properties, molecular size, behavior in HeLa cell culture and in the used CM-cellulose chromatography system all link FTC to the "R-group" of B binders. The B binding protein in human milk (Finkler *et al.* 1967) may belong to "R-group" as well although immunological evidence is lacking. Stenman and co-workers (1968) showed that the "R binders" of different origin differ as to their molecular electric charge. They ascribe this to the differences in sialic acid contents. The same concept may apply to FTC.

What then is the role of FTC in the previously well-organized family of serum B_{12} binders? It is clear that it does not share the carrying of native B_{12} with TC I. The *in vitro* studies indicate that it has the same properties as previously described for TC II in not containing B_{12} but being able to bind added B_{12}. However TC II has been shown both *in vivo* and *in vitro* to deliver its B to cells and tissues (Hall and Finkler 1965, Finkler and Hall 1967, Hom 1967b). No such function for FTC was demonstrated by the present HeLa cell culture studies. This does not rule out the possibility that FTC could, under different circumstances or with other types of cells, act as a carrier of B to body cells. The B uptake from the binders has been shown to be tissue specific by experiments using intrinsic factor and the R-binders of serum, leukocytes and gastric juice (Simons *et al.* 1966). It was shown that guinea pig intestine homogenate took up B from intrinsic factor complex but not from R-binder complex, whereas the reverse was true for rat liver homogenate. These studies were performed using heterologous systems which reduces their value. It should also be noted here that in the work cited above the serum R-binder equals TC II. To get a firmer basis for the speculation concerning the function of FTC would necessarily require *in vivo* studies.

It is interesting to note that there is one serum B binder which resembles FTC in all its studied properties. This is the B binder in polycythemia vera serum (Hall and Finkler 1967). It does not carry endogenous B but binds added B. Its behavior in DEAE and CM-cellulose chromatographies is the same as that of FTC, it has an intermediate electrophoretic mobility when compared to TC I and TC II and it has a large molecular size. It does not promote the uptake of B by HeLa cells. Furthermore the polycythemia vera binder reacts with an antiserum produced against TC I (Finkler *et al.* 1968). It is an interesting analogy that in some cord and

neonatal sera and in a small number of maternal sera immediately after delivery a protein which was antigenically similar to a protein found in some malignant diseases, has been detected (Takahashi *et al.* 1967). This protein has no known correlation with vitamin B_{12}.

A starting point for the present work was the difference in B_{12} concentrations between cord serum and maternal serum. The most interesting result of the experiments was the description of a new B_{12} binder which is called FTC. It does not give any explanation for the difference in B_{12} serum concentrations, because it does not contain native B_{12}. The possible explanation for the initiating problem could be the native B_{12} found in cord serum TC II. This aspect was not explored further since with the discovery of FTC the work was focused on the characterization of it. Whether FTC has anything to do with the transplacental passage and concentration gradient of vitamin B_{12}, remains to be elucidated by further work.

Summary

The serum binding of vitamin B_{12} in the newborn infant was studied using *in vitro* labeling of serum proteins with CoB_{12} and ionic exchange chromatography for the separation of B_{12} binders. As to the carrier of native B_{12}, TC I, no differences were found when adult and cord sera were compared. For the binder of exogenous or "new" B_{12}, TC II, one previously unreported phenomenon was detected in cord serum: TC II was found to contain native or endogenous B_{12}. A third B_{12} binder, which was designated fetal transcobalamin or FTC, was found in cord serum. FTC dit not contain native vitamin B_{12}, but it bound *in vitro* added vitamin B_{12}. FTC had the same molecular size with TC I (molecular weight around 120 000) and its electrophoretic mobility was between TC I and TC II at pH 8.6 and pH 4.5. $^{57}CoB_{12}$ bound to FTC was not taken up by HeLa cell cultures. The studied serum samples from infants did not permit any definite conclusions about the "normalization" of the newborn B_{12} binding pattern, although binding of added B_{12} to FTC diminished with age. Part of the studied maternal sera contained a binder similar to FTC as judged by DEAE-chromatography. The possible similarity between FTC and a minor binder in some adult sera was discussed. A suggestion was made that FTC belongs to the "R-group" of B_{12} binders by the terminology of Simons (1964). No specific function for FTC could be clarified by the present *in vitro* studies.

References

1. Agunod, M. B., Yamaguchi, N., Lopez, R., Cooperman, J. M. and Lobby, A. L.: Intrinsic factor, acid and pepsin secretion in newborn infants. *Fed Proc 26*: 33, 1967
2. Andrews, P.: Estimation of the molecular weights of proteins by Sephadex gel filtration. *Biochem J 91*: 222—233, 1964.
3. Baker, H., Erdberg, R., Pasher, I. and Sobotka, H.: Study on folic acid and vitamin B_{12} in blood and urine during normal pregnancy. *Proc Soc Exp Biol Med 94*: 513—514, 1957
4. Baker, H., Ziffer, H., Pasher, I. and Sobotka, H.: A comparison of maternal and foetal folic acid and vitamin B_{12} at parturition. *Brit Med J 1*: 978—979, 1958.
5. Baker, S. J., Jacob, E., Rajan, K. T. and Gurunathan, R. P.: Vitamin B_{12} deficiency in pregnancy and the puerperium. *Brit Med J 1*: 1658—1661, 1962.
6. Ball, E. W. and Giles, C.: Folic acid and vitamin B_{12} levels in pregnancy and their relation to megaloblastic anaemia. *J Clin Path 17*: 165—174, 1964.
7. Banerjee, D. K., Ghosh, H. K. and Chatterjea, J. B.: Observations on the binding of vitamin B_{12} by serum proteins (with a note on the effect of some electrophoresis on the availability of vitamin B_{12} to Euglena gracilis). *Indian J Med Res 51*: 264—276, 1963.
8. Bar-Shany, S. and Herbert, V.: Transplacentally acquired antibody to intrinsic factor with vitamin B_{12} deficiency. *Blood 30*: 777—784, 1967
9. Beard, M. F., Pitney, W. R. and Sanneman, E. H.: Serum concentrations of vitamin B_{12} in patients suffering from leukemia. *Blood 9*: 789—794, 1954
10. Boass, A. and Wilson, T. H.: Development of the mechanisms for intestinal absorption of vitamin B_{12} in growing rats. *Amer J Physiol 204*: 101—104, 1963
11. Boger, W. P., Wright, L. D., Beck, G. D. and Bayne, G. M.: Vitamin B_{12}: correlation of serum concentrations and pregnancy. *Proc Soc Exp Biol Med 92*: 140—143, 1956.
12. Boger, W. P., Wright, L. D. and Bayne, G. M.: Serum vitamin B_{12} concentrations of pregnant women and newborn infants. In: *Vitamin B_{12} and Intrinsic Factor*. 1. Europäisches Symposion, Hamburg 1956, pages 443—449. Ferdinand Enke, Stuttgart 1957.
13. Boger, W. P., Bayne, G. M., Wright, L. D. and Beck, G. D.: Differential serum vitamin B_{12} concentrations in mothers and infants. *New Engl J Med 256*: 1085—1087, 1957b.
14. Chow, B. F., Barrows, L. and Ling, C. T.: The distribution of radioactivity in the organs of the fetus or of young rats born by mothers injected with vitamin B_{12} containing Co^{60}. *Arch Biochem 34*: 151—157, 1951
15. Chow, B. F., Hsu, J. M., Okuda, K., Grasbeck, R. and Horonick, A.: Factors affecting the absorption of vitamin B_{12}. *Amer J Clin Nutr 6*: 386—393, 1958.
16. Chow, B. F. and Okuda, K.: Transfer of vitamins from mother to fetus. *JAMA 172*: 423—426, 1960.
17. Cohen, F., Zuelzer, W. W., Gustafson, D. C. and Evans, M. M.: Mechanisms of isoimmunization. I. The transplacental passage of fetal erythrocytes in homospecific pregnancies. *Blood 23*: 621—646, 1964.
18. Cooper, B. and Paranchych, W.: Selective uptake of specifically bound cobalt-58 vitamin B_{12} by human and mouse tumor cells. *Nature 191*: 393—395, 1961
19. Danesino, V. and Montemagno, U.: Indagini scintillometriche sul passaggio transplacentare della B_{12}-^{60}Co. *Arch Ostet Ginec 66*: 9—48, 1961.
20. Dixit, C. H., Mody, B. N., Jhala, H. L., Parikh, J. G. and Ramanayya, G. B.: A note on serum vitamin B_{12} concentrations in parturient mothers and the cord blood of their infants. *Indian J Med Res 11*: 143—146, 1957
21. Donnet, M. and Karlin, R.: Étude de la teneur en vitamine B_{12} du placenta du sang maternel et du sang foetal dans l'accouchement à terme et prématuré. *Gynéc Obstét (Paris) 56*: 197—201, 1957
22. Flakier, A. E. and Hall, C. A.: Nature of the relationship between vitamin B_{12} binding and cell uptake. *Arch Biochem 120*: 79—85, 1967

Summary

The serum binding of vitamin B_{12} in the newborn infant was studied using *in vitro* labeling of serum proteins with $^{57}CoB_{12}$ and ionic exchange chromatography for the separation of B_{12} binders. As to the carrier of native B_{12}, TC I, no differences were found when adult and cord sera were compared. For the binder of exogenous or "new" B_{12}, TC II, one previously unreported phenomenon was detected in cord serum. TC II was found to contain native or endogenous B_{12}. A third B_{12} binder, which was designated fetal transcobalamin or FTC, was found in cord serum. FTC dit not contain native vitamin B_{12}, but it bound *in vitro* added vitamin B_{12}. FTC had the same molecular size with TC I (molecular weight around 120 000) and its electrophoretic mobility was between TC I and TC II at pH 8.6 and pH 4.5. $^{57}CoB_{12}$ bound to FTC was not taken up by HeLa cell cultures. The studied serum samples from infants did not permit any definite conclusions about the "normalization" of the newborn B_{12} binding pattern, although binding of added B_{12} to FTC diminished with age. Part of the studied maternal sera contained a binder similar to FTC as judged by DEAE-chromatography. The possible similarity between FTC and a minor binder in some adult sera was discussed. A suggestion was made that FTC belongs to the "R-group" of B_{12} binders by the terminology of Simons (1964). No specific function for FTC could be clarified by the present *in vitro* studies.

References

1. Agamal, M. B., Yamaguchi, N., Lopez, R., Cooperman, J. M. and Lobby, A. L. Intrinsic factor and pepsin secretion in newborn infants. *Fed Proc 26* 224, 1967

2. Andrews, P. Estimation of the molecular weights of proteins by Sephadex gel filtration. *Biochem J 91* 222—233, 1964

3. Baker, H., Erdberg, R., Pasher, I. and Sobotka, H. Study on folic acid and vitamin B_{12} in blood and urine during normal pregnancy. *Proc Soc Exp Biol Med 94* 513—515, 1957

4. Baker, H., Ziffer, H., Pasher, I. and Sobotka, H. A comparison of maternal and foetal folic acid and vitamin B_{12} at parturition. *Brit Med J 1* 978—979, 1958.

5. Baker, S. J., Jacob, E., Rajan, K. T. and Swaminathan, S. P. Vitamin B_{12} deficiency in pregnancy and the puerperium. *Brit Med J 1* 1658—1661, 1962.

6. Ball, E. W. and Giles, C. Folic acid and vitamin B_{12} levels in pregnancy and their relation to megaloblastic anaemia. *J Clin Path 17* 165—174, 1964.

7. Banerjee, D. K., Ghosh, B. K. and Chatterjea, J. B. Observations on the binding of vitamin B_{12} by serum proteins (with a note on the effect of some electrophoresis on the availability of vitamin B_{12} to Euglena gracilis). *Indian J Med Res 51* 264—276, 1963.

8. Bar-Shany, S. and Herbert, V. Transplacentally acquired antibody to intrinsic factor with vitamin B_{12} deficiency. *Blood 30* 777—784, 1967

9. Beard, M. F., Pitney, W. R. and Sanneman, E. H. Serum concentrations of vitamin B_{12} in patients suffering from leukemia. *Blood 9* 789—794, 1954.

10. Boass, A. and Wilson, T. H. Development of the mechanisms for intestinal absorption of vitamin B_{12} in growing rats. *Amer J Physiol 204* 101—104, 1963.

11. Boger, W. P., Wright, L. D., Beck, G. D. and Bayne, G. M. Vitamin B_{12}: correlation of serum concentrations and pregnancy. *Proc Soc Exp Biol Med 92* 140—143, 1956.

12. Boger, W. P., Wright, L. D. and Bayne, G. M. Serum vitamin B_{12} concentrations of pregnant women and newborn infants. In: *Vitamin B12 and Intrinsic Factor*. 1. Europäisches Symposion, Hamburg 1956, pages 443—449. Ferdinand Enke, Stuttgart 1957.

13. Boger, W. P., Bayne, G. M., Wright, L. D. and Beck, G. D. Differential serum vitamin B_{12} concentrations in mothers and infants. *New Eng J Med 256* 1085—1087, 1957

14. Chow, B. F., Barrows, L. and Ling, C. T. The distribution of radioactivity in the organs of the fetuses of young rats born by mothers injected with vitamin B_{12} containing Co^{60}. *Arch Biochem 34* 151—157, 1951

15. Chow, B. F., Hsu, J. M., Okuda, K., Grasbeck, R. and Horonick, A. Factors affecting the absorption of vitamin B_{12}. *Amer J Clin Nutr 6* 386—392, 1958.

16. Chow, B. F. and Okuda, K. Transfer of vitamin from mother to fetus. *JAMA 172* 422—425, 1960.

17. Cohen, F., Zuelzer, W. W., Gustafson, D. C. and Evans, M. M. Mechanisms of isoimmunization. I. The transplacental passage of fetal erythrocytes in homospecific pregnancies. *Blood 23* 621—646, 1964

18. Cooper, B. and Paranchych, W. Selective uptake of specifically bound Cobalt 58 vitamin B_{12} by human and mouse tumor cells. *Nature 191* 393—395, 1961

19. Danesino, V. and Montemagno, U. Indagini scintillometriche sul passaggio transplacentare della B_{12}-^{58}Co. *Arch Ost Ginec 66* 92—95, 1961

20. Dixit, C. H., Modi, B. N., Jhala, H. I., Parekh, J. G. and Ramasarma, G. B. A note on serum vitamin B_{12} concentrations in parturient mothers and the cord blood of their infants. *Indian J Med Res 11* 143—146, 1957

21. Dumont, M. and Karlin, R. Étude de la teneur en vitamine B_{12} du placenta du sang maternel et du sang foetal dans l'accouchement à terme et prématuré. *Gynéc Obstét (Paris) 56* 197—201, 1957

22. Finkler, A. E. and Hall, C. A. Nature of the relationship between vitamin B_{12} binding and cell uptake. *Arch Biochem 120* 79—85, 1967

23. Finkler A. E., Rappazzo, M. and Hall, C. A. Cyanocobalamin binding protein in human milk. *Fed Proc 26*: 693 106

24. Finkler A. E., Hall, C. A., Green, P D and Young C. C. Immunologic studies of vitamin B_{12} binding proteins. *Fed Proc 27*: 76, 1968.

25. Gabrazin T G Worm Petersen, J and Lous, P The binding of vitamin B_{12} added *in vitro* and *in vivo* to normal human serum proteins separated on ion excha ge cellulose. *Scand J Haemat* 61—66, 1965.

26. Giles, C. An account of 335 cases of megaloblastic anaemia of pregnancy and the puerperium. *J Clin Path 19*: 1—11 1966.

27. Goldberg L. S., Barnett E. V and Desai, R.: Effect of transplacental transfer of antibody to intrinsic factor *P diatrics 40*: 851—855, 1967

28. Gotchel, R. I and Lovett B. F Vitamin B_{12} absorption during pregnancy a controlled study *Amer J Obst t Gyneo 79*: 113—116, 1960

29. Gräsbeck, R.: Intrinsic facto and the transcobalamins with reflections on the general function and evolution of soluble transport proteins. *Scand J Clin Lab I vest 19 suppl. 95*: 7—18, 1967

30. Hall, C. A. and Finkler A E.: *In vivo* plasma vitamin B_{12} binding in B_{12} deficient and no deficient subjects. *J Lab Clin Med 60*: 765—776, 1962.

31. Hall, C. A., Kulonen M. and Oka M.: The plasma disappearance f i travenous Cobalt 57 vitamin B_{12} in it min B deficiencies. *A ta M d Scand 171*: 147—150 1962.

32. Hall, C. A. an l Finkler A. E.: A second itamin B_{12} binding substance in human plasma. *B och m B phys Acta 78* 233—236, 1963.

33. Hall, C. A. and Allen, E. S.: Improved method for the extraction of itamin B_{12} from serum. *J Lab Cl n Med 64*: 517—5.3, 1964.

34. Hall, C. A. and Finkle A. E Abnormal transport of vitamin B_{12} in plasma in chronic myelogenous leukemia. *Nat re 204* 1207 1964

35. Hall, C. A. and Finkler A. E.: The dynamics of transcobalamin II. A itamin B_{12} binding substance in plasma. *J Lab Clin Med 65* 459—468, 1965

36. Hall, C. A and Finkler A. E. Measurement of the amounts of the individual vitamin B_{12} binding proteins in plasma. I Studies on normal plasma. *Blood 27* 611—617 1966a.

37. Hall, C. A. and Finkler A. E. Measurement of the amounts f the individual vitamin B_{12} binding proteins in plasma. II. Abnormalities in leukemia and pernicious anemia. *Blood 2* 618—622, 1966b.

38. Hall, C. A. *Personal communication* 1967

39. Hall, C. A. and Finkler A. E.: A vitamin binding protein in polycythemia vera plasm *B ochim Biophys Acta 147* 156—158, 1967

40. Hansen, H. A.: Folic acid, B_{12}-vitamin serum Fe under den normala graviditeten. *Med 61* 843, 1959

41. Hardwicke, J and Jones, J H: The nature the vitamin B_{12} binding protein in human seru *Brit J Haemat 12* 529—535, 1966.

42. Haught J E., Strickland, J E. and Miller N: Production of plasma B_{12} transport substance transcobalamin II by the isolat perfused rat liver *Amer J Clin Nutr 20*: 371 37., 1967

43. Heinrich, H C.: Die biochemischen Grundlag der Diagnostik und Therapie der Vitamin B Mangelzustände des Menschen und der Haustie II. Untersuchu gen zum Vitamin B_{12}-Stof wechsel des Menschen während der Gravidit und Lactation. *Klin Wschr 32*: 205—209, 19

44. Hellegers, A., Okuda, K., Nesbitt R. E. Smith, D W nd Chow B. F: Vitamin B absorptio in pregnancy and in the newbor *Amer J Cl n Nut 5*: 327—331 1957

45. H m, B., Olesen, H and Lous, P: Fractionati of vit min B_{12} bi ders in human serum. *J L Clin Med 68* 958—965, 1966.

46. Hom, B. Demonstration of transcobalamin complex formation and binding to Sephade G-200 at low ionic stre gth. *Clin Chim Acta 1* 315—317 1967a.

47. Hom, B.: Plasma turnover of ^{57}Cobalt Vitam B_{12} bound to transcobalamin I and II *Scand Haemat 4*: 3.1—332, 1967b.

48. H m, B. and Olesen, H. Molecular weights vitamin B_{12} binding prot ins in huma seru determined by Sephade G-200 gel filtratio *Scand J Cl n Lab I ve t 19* 269—273 1967

49. Hom, B and Ahluwalia, B. K The vitamin B binding capacity of transcobalamin I and II o normal human serum. *Scand J Haemat 5*: 64—74 1968.

50. Hom B Olesen, H. and Schwartz, M Turnove of ^{57}Co-labelled itami B_{12} transcobalamin I and tologous ^{131}I labelled IgG in patie with antibody to transcobalamin II. *Scand J Haemat 5* 107—115, 1968.

51. Jäykkä, S. The anatomical changes in the hepatic arteriole at birth. A possible relation ship bet een the circulatory transition and the development f neonatal jaundice. *Biol Neonat 7* 313—318, 1964.

52. Jones, C. C., Brown, S. O., Richardson, L. R. and Sinclair J. G. Tissue abnormalities in newborn rats from vitamin B_{12} deficient mothers. *Proc Soc Exp Biol Med 90* 13—140, 1955.

53. Karlin, R. Sur la vitamine B_{12} et la méthionine du sérum sanguin chez la femme pendant la gestation et la lactation. *C R Soc Biol. (Paris) 149* 971—9 4, 1955.

54. Karlin, R. and Dumont, M. Sur le taux de vitamine B_{12} dans le sérum sanguin chez la femme au cours de l'accouchement, dans celui du cordon et dans le placenta. *C R Soc Biol (Paris) 149* 1956—1955, 19...

55. Karlin, R. Étude sur la répartition de la vitamine B_{12} sérique hépatique et placentaire au cours de la vie intra utérine du Cobaye. *C R Soc Biol (Paris) 150* 1211—1213, 19.6.

56. Karlin, R. Effet de l'administration orale ou parentérale de la vitamine B_{12} sur sa répartition et mise en réserve au cours de la le intra-utérine du Cobaye. *Bull Soc Chim Biol (Paris) 39* 1001—1004, 1957

57 Killander A. and Vahlquist, B. B_{12}-vitaminkoncentrationen i serum från fullgångna och prematurt födda barn. *Nord Med 51* 777—779 1954.

58. Killander A The serum vitamin B_{12} levels at various ges. *Acta Paediat (Uppsala) 46* ...—...4, 1957

59. Killander J The vitamin B_{12} content of human fetal tissues *Acta Chem Scand 11* 13..6, 19.6.

60. Kumento, A., Leyes, R., Lahby A. L. and Hall, C A. B_{12} binders in human cord serum. *Clin Res 15* 2.3, 1967

61 Lawrence C. B_{12} binding protein deficiency in pernicious anemia. *Blood 27* 389—394, 1966.

62. Lawrence C. and Klipstein, F Megaloblastic anemia of pregnancy in New York City *Ann Intern Med 66* 2.—34, 1967

63 Layrisse M., Aguero, O Blumenfeld, N Wallis, H., Dugarte, I. and Ojeda, A. Megaloblastic anemia of pregnancy characteristics of pure megaloblastic anemia and megaloblastic anemia associated with iron deficiency *Blood 15* 724—740, 1960.

64 Lepkovsky S., Borson, H. J Bouthilet, R., Pencharz, R., Singman, D., Dimick, M. K and Robbins, R. Reproduction in vitamin B_{12}-deficient rats with emphasis upon intrauterine injury *Amer J Physiol 165* 79—86, 1951.

65 Lowenstein, L. Lalonde, M., Deschenes, E. and Shapiro, L. Vitamin B_{12} in pregnancy and the puerperium. *Amer J Clin Nutr 8* 265—275, 1960.

66. Lowry O. H., Rosebrough, N J Farr, A. L. and Randall, R. J Protein measurement with the Folin phenol reagent. *J Biol Chem 193* 265—275, 1951

67 Lahby A. L., Cooperman, J Donnenfeld, A., Herrera, J Teller J and Wenig, J: Observations on transfer of vitamin B_{12} from mother to fetus and newborn. *Amer J Dis Child 96* 532, 1958.

68. Lahby A. L., Cooperman, J Herrera, J and Donnenfeld, A. New concept regarding maternal cyanocobalamin (vitamin B_{12}) available for placental transfer *Arch Dis Child 33*: 619, 1958a.

69. Lahby A. L., Cooperman, J and Donnenfeld, A. Placental transfer and biological half life of radioactive vitamin B_{12} in the dog. *Proc Soc Exp Biol Med 100* 214—217 19..9b.

70. Lahby A. L., Cooperman, J Stone M. and Slobody L. Physiology f vitamin B_{12} i pregnancy the placenta and the newborn. *Amer J Dis Child 101* 753—754, 1961a.

71. Lahby A. L., Feldman, R., Marley J Odang, O. and Cooperman, J Serum vitamin B_{12} in infancy *Fed Proc 20* 451, 1961b.

72. Lust, J E., Hagerman, D. D and Villee, C. A. The transport of riboflavin by human placenta. *J Clin I est 33* 38—40, 19.4.

73. Mendelsohn, R. S., Watkin, D. M., Horbett, A. P and Fahey J L Identification f the vitamin B_{12} binding protein in the serum of normals and of patients with chronic myelocytic leukemia. *Blood 13* 740—747 19.8.

74. Meyer L., Cuofsky M. and Miller L.: Plasma clearance of $Co^{60}B_{12}$ in pernicious anemia. *Scand J Clin Lab I vest 19* ppl. 95 37 1967

75. Mikkonen, L., Fiakler A. L. and Hall, C. A. A diagnostic test for chronic myelogenous leukemia based on abnormalities of B_{12} binding *Acta Med Scand 181* .91—396, 1967

76 Miller A. The in vitro binding of Co^{60} labeled vitamin B_{12} by normal and leukemic sera. *J Clin Invest 37* 5..6—..66, 19.8.

77 Miller A. and Sullivan, J Some physicochemical properties f the vitamin B_{12} binding substances f normal and chronic myelogenous leukemic sera. *J Lab Clin Med 45* 607—616, 19..9a.

78. Miller A. and Sullivan, J Electrophoretic studies f the vitamin B_{12} binding protein f normal and chronic myelogenous leukemia serum. *J Clin I vest 38* 2135—2143, 1959b.

79 Nesbitt, R. E. and Chow B. F Vitamin B_{12} in pregnancy and in the newborn. *Obstet Gynec Survey 13* 461—472, 19.8.

80. Okuda, K., Hellegers, A. E. and Chow B. F

–3. Finkler A. E., Rappazzo, M. and H ll, C. A. Cyanocobalamin binding protein in human milk. *Fed Proc 26* 695 1967

4. Finkler A. E., Hall, C. A Green, P D and Young, C. C.: Immunologic studies of vitamin B_{12} binding proteins. *Fed Proc 27*: °76, 1968.

–5. Gabuzda T G Worm Petersen, J and Lous, P The l inding of itamin B_{12} added *in vitro* and *in vivo* to normal human serum proteins sepa rated on ion exchange cellulose *Scand J Haemat 2*: 61—66, 1965.

26. Giles, C.: An account of 335 cases of megaloblastic anaemia of pregnancy d the puerperium. *J Clin P th 19*: 1—11 1966.

7 Goldberg, L. S., Barnett E. V d Desai, R.: Effect of transplacental transfer of antibody to intrinsic factor *Pediatrics 40* 851—853 1967

28. Gotchel, R. P and Lovett, B. F : Vitamin B_{12} absorption during pregnancy a controlled study *Amer J Obstet Gynec 79* 113—116, 1960

°0 Gräsbeck, R.: Intrinsic factor and the transcobalamins; with reflections on the general function and evol tion f soluble transport proteins. *Scand J Cl n Lab I vest 19* ppl. 95 7—18, 1967

30 Hall, C. A. and Finkler A. E. *In vivo* plasma vitamin B_{12} binding in B_{12} deficient and nondeficient subjects. *J Lab Clin Med 60*: 765—6, 1962.

31 Hall, C A., Kulonen, M and Oks M The plasma disappearance of intrave ous Cobalt-57 vitamin B_{12} in itamin B_{12} deficiencies. *Acta Med Scand 171*: 147—150 196—

32. Hall C. A. an l Finkle A E. A second vitamin B_{12} binding subst nce in human plasma. *B ochim B ophys Acta 8*: 233—236, 1963.

33. Hall, C. A. and Allen, E. S.: Improved method for the extraction of vitamin B_{12} from serum. *J Lab Cl n Med 63* 317—523, 1964.

34. Hall C. A. and Finkle A E. Abnormal transport of vitamin B_{12} in plasma in hronic myelogenous leukemia. *Nature 204* 1207 1964

35. Hall, C. A. and Finkle A. E.: The dynamics of transcobalamin II A vitamin B_{12} binding substance in plasma. *J Lab Cl n M d 65* 459—468, 1965.

36. Hall, C. A n d Finkler A L Measurement of the amounts of the individual vitamin B_{12} bindi g proteins in plasma. I. Studies on normal plasma. *Blood 27* 611—617 1966a.

37 Hall, C. A. nd Finkler A. E. Measurement of the amounts f the indi idual vitamin B_{12} binding proteins in plasma. II Abnormalities in leukemia and pernicious anemia. *Blood* ❞ 618—622, 1966b.

38. *Hall, C. A.: Personal communicat* 1967

39 Hall, C. A. and Finkler A. E.: A vitamin B_{12} binding protein in polycythemia vera plasma. *Bioch m Biophys Acta 147*: 186—188, 1967

40. Hansen, H A.: F lic acid, B_{12} vitamin och serum Fe unde den normala graviditeten. *Nord Med 61*: 84—, 1959

41 Hardwicke J and Jones, J H. The nature of the vitamin B_{12} binding protein in human serum. *Brit J Haemat 12*: 529—535, 1966.

4— Haught J L., Strickland, J E. and Miller O. N : Production of plasma B_{12} transporting substance transcobalamin II by the isolated perfused rat liver *Amer J Cl n Nutr °0* 3 1—373, 1967

43. Heinrich, H. C.: Die biochemischen Grundlagen der Diagnostik und Therapie der Vitamin B_{12} Mangelzustände des Menschen und der Haustiere II. Untersuchungen zum Vitamin B_{12}-Stoff wechsel des Mensche während der Gravidität u d Laktation. *Klin Wschr 33* °05—209, 1954.

44. Hellegers, A., Okuda K., Nesbitt R. E. L., Smith, D W and Chow B. F Vitamin B_{12} absorption I pregnan y nd in the newborn. *Amer J Clin N t 5* 327—331 1957

45. Hom, B., Olesen, H and Lous, P : Fractionation of vitamin B_{12} binders in human serum. *J Lab Cl n Med 68*: 958—965, 1966.

46. Hom, B.: Demonstration of transcobalamin II complex formation and binding to Sephadex G °00 at low ioni strength. *Clin Chim Acta 18*: 315—317 1967a.

47 Hom, B. Plasma turnover of ⁵⁷Cobalt Vitamin B_{12} bound to transcobalami I and II *Scand J H emat 4*: 321—33—, 1967b.

48. Hom, B. and Olesen, H. M lecular weights of vitamin B_{12} binding proteins in human serum determined by Sephadex G-°00 gel filtration. *Scand J Cli Lab In est 19* 269—°73, 1967

49 Hom, B. and Ahluwalia, B. K : The vitamin B_{12} binding capacity f transcobalamin I and II of ormal human serum. *Scand J Haemat 5* 64—74 1968.

50. Hom B., Olesen, H and Sch artz, M Turnover of ⁵⁷Co-labelled vitamin B_{12} transcobalamin II and tologous ¹²⁵I labelled IgG i a patient with antibody to transcobalamin II *Scand J Haemat 5* 10 —115 1968.

51 Jäykkä, S.: The anatomical ha ges in the hepatic arteriole t birth. A possible relation ship between the circulatory transition nd the dev lopment of neonatal jaundice *Biol N onat 7* 313—318, 1964.

olism of transcobalamin II. *Fed Proc 26*: 685, 1967

108. Weinstein, L., Weissman, S. and Watkin, D. The plasma vitamin B_{12} binding substance. I. Its detection from the seromucoid fraction of plasma from normal subjects and patients with chronic myelocytic leukemia. *J Clin Invest 38*: 1904—1914, 1959.

109. Wilson, T. H. The development of vitamin B_{12} and amino acid absorption by the small intestine. *Biol Neonat 9*: 63—72, 1965/66.

110. Wöhler, F. Intermediary iron metabolism of the placenta, with special consideration of the transport of therapeutically administered iron through this organ. *Curr Ther Res 6*: 464—482, 1964.

111. Woodard, J. C. and Newberne, P. M. The pathogenesis of hydrocephalus in newborn rats deficient in vitamin B_{12}. *J Embryol Exp Morph 17*: 177—15?, 1967

112. Woods, W. D., Hawkins, W. B. and Whipple, G. H. Vitamin B_{12} readily passes the placenta into fetal organs and nursing provides B_{12} from mother to pup. *J Exp Med 112*: 431—444, 1960.

113. Young, J. E., Barrows, C. Jr., Okada, K. and Chow, B. F. Vitamin B_{12} serum level in pregnancy. *Obstet Gynec 16*: 149—153, 1960.

114. Zachau-Christiansen, B., Hoff-Jørgensen, E. and Østergård Kristensen, H. The relative haemoglobin, iron, vitamin B_{12} and folic acid values in the blood of mothers and their newborn infants. *Danish Med Bull 9*: 157—166, 1962.

Vitamin B_{12} serum level and pregnancy. Amer J Clin N tr 4: 440—443, 1956.

81 Olesen, H., Hom, B. and Schw rtz, M: Antibody to TC II in patient treated with long-acting vitamin B_{12} preparations. Scand J Haemat 5: 5—16, 1968.

82. Peltonen, T and Hirvonen, L.: Effect of exchange transfusion on the protein-bound Iodine in the newborn infant. Ann Acad Sci Fenn (Med) 106/14 1—8, 1964

83. Peltonen, T and Hirvonen L.: Protein-bound Iodine in the newborn infant. Acta Paed t Scand suppl. 159: 141 1965

84 Peterson A. E. and Chiazze E. A.: Some experimental factors i the gradient chromatography of serum proteins. Arch Biochem 99: 136—147 196..

85 Pitney W R Beard, M and Van Loon, E.: Observations on the bound form of vitamin B_{12} i human serum. J Biol Chem 207: 143—15.., 1954

86. Prystowsky H., Hellegers, A E., Ranke E., Ranke B a d Chow B F: Further observations on the metabolism of vitamin B_{12} i human pregnancy. Amer J Obstet Gynec 77: 1—5, 1959

87 Räihä, N On the placental transfer of vit min C. An experimental study on guinea pigs and human subjects. Acta Physiol Scand 45 suppl. 155 1—53, 1958.

88. Rappazzo M Salmi, H A. d Hall, C. A: Unpublished results 1968.

89 Retief F Gottlieb, C. W Kochwa, S., Pratt P and Herbert V Separation of vitamin B_{12} binding proteins of serum, gastric juice and saliva by rapid DEAE-cellulose chromatography. Blood 29 501—516, 1967a.

90 Retief F Gottlieb, C. W and Herbert V Delivery of $Co^{57}B_{12}$ to erythrocytes from alpha and beta globulin of normal, B_{12}-deficient and chronic myeloid leukemia serum. Blood 29: 837—851 1967b.

91 Rice E. G H rndon, J F Van Loon E. J and Greenberg, S. M Enhancement of itamin B_{12} absorption by D-sorbitol as measured by maternal and f t l tissue levels i pregnant rats. Amer J Physiol 193 513—515, 1958.

92. Sadovsky A., Berecovici, B., Bachmilewitz, M., Grossowicz, N and Aronovitch, J Vitamin B_{12} concentration in maternal and fetal blood. Obst t Gyne 13: 346—349 1959

93. Sahi, S., Tan, C., Miller O N d Hansen, H. J Effects f puromycin and cycloheximide n the synthesis f itamin B_{12} binders in the mouse. Fed Proc 26: 695 1967

94 Salmi, H. A.: Comparative studies on vitamin B_{12} in developing organism and placenta. Human and animal investigations with reference to the effects of low vitamin B_{12} diet on tissue vitamin B_{12} concentration in rat. Ann Acad Sci Fenn (Med) 103: 1—91 1963.

95. Salmi H. A. Absorption of radioactive cyanocobalamin from the developi g digestive canal. Acta Physiol Scand 68 suppl. 277: 1 3, 1966.

96. Satoskar R. S., Kulkarni B. S., Mehta, B M. and Parikh, M V: Maternal and foetal serum vitamin B_{12} and folic acid levels in Indian subjects. J Obstet Gynaec Brit Comm 68 930—933, 1961

97 Schellong, G: in Ikterus neonat r m (pages 18—19 Georg Thieme Verlag, Stuttgart 1962.

98. Schwartz, M and Bastrup-Madsen, P: A new vitamin B_{12} binding protein i serum causing excessi ely high serum vitamin B_{12} values. Scand J Haemat 5: 33—40 1968.

99. Simons, K. Vitamin B_{12} binders in human body fluids and blood cells. Soc Scient Fen ica C mm B ol 27 fasc 5 1964

100 Simons, K., Krist G. and Saurén-Li dfors, M: The effect of purified vitamin B_{12} binding proteins on the uptake of itamin B_{12} i tissues. Ann Med Exp B ol Fenn 44: 361—366, 1966.

101 Ståhlberg K. G Radner S. and Nordén, A. Li er B_{12} in subjects with nd without vitamin B_{12} deficiency A quantit ti and qualit ti study Scand J Haemat 4 31 —320, 1967

10.. St nman U H., Simons, K. and Gräsbeck, R.: Immunochemical chara terization of transcobalamins in normal nd leukemic human leukocytes and se a. Sca d J Cl n Lab Invest 19 suppl. 95 36, 1967

103. Stenman, U H Simons, K. nd Gräsbeck, R. The ffect of neuraminidase on human transcobalamin I and leukocyt vit min B_{12} binding protein. Scand J Cl Lab I vest 21 ppl. 101 13, 1968.

104. Sullivan, L. W Greene R. J nd Liu, Y K.: Serum itamin B_{12} binding capacity in pregnancy The 59th nn l me t g f America Society f Cl nical I vest gat Atla tic City N.J 1967

10.. T kahashi A., Y chi, A Anzai, T l W da, T Presence f ique serum protei in sera obtained from pat nt with neoplastic diseases and in embryonic d neonatal sera. Cl Ch m Acta 17 5—12, 1967

106. Ta C. d Hansen, H I vitro transfer of itamin B_{12} from mouse intrinsic f tor t mouse transcobalamin II. Cl n Res 14 437 1966.

107 Ta C., Mill O N and Hansen, H. Metab-

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 193 1969

GROUPS AT RISK IN LOW BIRTH WEIGHT INFANTS AND PERINATAL MORTALITY

BY PAULA RANTAKALLIO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge

131 Mellbin, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw kr. 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw kr 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw kr. 25.— 1962
134. Möller Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr 25.— 1962
135. *I Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet*, June 30, 1962. Sw kr 25.— 1962
136. Bille Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and clinical, psychological and electroencephalographic comparison between children with migraine od matched controls. Sw. kr 25.— 1962
137 Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr 25.— 1962
138. Wallgren, Eric Ivar Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw kr 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia nd Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen. 1961. Edited by E. Winge Flensborg. Sw kr. 30.— 1963
141. Wasz-Höckert, Ole and Donner Mårta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and socio-medical study. Sw kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy A Clinical and Experimental Study Sw. kr. 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P Nylander L, Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Bervan, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply Sw. kr 20.— 1963
149. Valaes, Tinos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw kr 25.— 1963
150. Mae, Peter Johan, Iron Requirements in Infancy Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151 *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw k — 1963
152. I- luries in Children
logy Therapy / 15.— 1964
Cardior Ataxia. With
Cardiovasc / Sw. kr
Mongo and Cytogene-
XI. Mechanism
in Asth-
Status. Sw. kr.
Paediatrics. Edi-
kr 25.— 1964
Glycogenosis
Siblings. T
kr.
in

161 Peltonen, T. and Hirvonen, L., Experimental and Neonatal Circulation. Sw. kr 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Prol. Health and in Haematological Disease during kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr
164. Böttiger, Margareta, Studies on Immunization with and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C Bronchiectasis A Review of 187 Cases in C up Pulmonary Function Studies in 58. Sw. kr. 20.—
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile toid Arthritis. Analysis of 544 Cases. Sw kr. 15.— 1
167 Iversen, Torben, Leukaemia rial of 370 Danish Cases. Sw kr. 30.— 1966
168. Trojaborg, W Focal Spike Discharges in Children nal Study Sw. kr 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30
171. Olding, Lars, Bacterial Infection in Cases of Perinat morphological and bacteriological study based on Sw. kr 20.— 1966
172. *Festschrift in Memory of Constantin Chevrent.* Sw.
173. Walsh, S. Zoe, The Esophageal Electrocardiogram First Week of Life. Sw kr 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Second clinical study before and after operation with to haemodynamic function. Sw. kr 25.— 1967
175. Hilmison, Fasti, Vectorcardiographic Studies in fants. Sw kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial V Sw. kr 20.— 1967
177 *Proceedings of the Fifteenth Northern Pediatric C* 1967 Sw. kr. 35.— 1967
178. Sjögren, Iréne, Echoencephalography in Paediatric Special Regard to Measurement of the Ventricul kr 25.— 1967
179. *Quantitative Studies of the Human* by Göran Wallgren. Sw kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the sponse to *E. Coli* O-Antigens in Infants and C Urinary Tract Infection, Using Passive Haem Technique. Sw. kr 20.— 1968
181. Koch, Gösta, Lung Function and Acid-Base Newborn Infant. Sw. kr 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A and Clinical Study. Sw. kr 25.— 1968
183. Robertson, Alex F and Sprecher, Howard, A Rev Placental Lipid Metabolism and Transport. Sw. kr
184. Robertson, Bengt, The intrapulmonary arterial pat infancy and in transposition of the great arteries. S 1968
185. Andersen, Elna, Skeletal Maturation in Relation to Height, Sexual Development, tions. Sw. kr 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-W of the Literature and Report of Nine Cases. Sw.
187 Karlberg, Petter, *et al.*, The Development of Ch dish Urban Community A Prospective Longitudina Sw. kr 30.— 1969
188. Mossetien, Gunnar W., and Molin, Kerstin, Studies Galactose Malabsorption. A Clinical Study of 6 Genetic Study Sw kr 25.— 1969
189 Fillström, S. P., On the Endogenous Formation Monoxide in Full-Term Newborn Infants. Sw. kr
190. Härnblad, P Yngve, Experimental Studies on Cl Ductus Arteriosus Utilizing Whole-Body Freez 1969
Antti, Cardiovascular Response of the Nec ia, Hypercapnia and Metabolic Acidosis. S
Lorna, Surveillance of Acute Viral Respi Sw kr 30.— 1969
Paula, Risk Groups of Low Birth Wei Mortality. 1969
Antti, Studies on the Serum Binding of Newborn Human Infant. Sw kr 30.— 1969

—

tryckeri AB Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 193 1969

GROUPS AT RISK IN LOW BIRTH WEIGHT INFANTS AND PERINATAL MORTALITY

BY PAULA RANTAKALLIO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

From the Department of Pediatrics, University of Oulu, Finland

GROUPS AT RISK IN LOW BIRTH WEIGHT INFANTS AND PERINATAL MORTALITY

A prospective study of the biological characteristics and socio-economic circumstances of mothers in 12,000 deliveries in North Finland 1966

A discriminant function analysis

By

Paula Rantakallio

OULU 1969

Translated by
Hilkka Kontiopää
Valerie Jansen

Printed in Finland
KIRJAPAINO OSAKEYHTIÖ KALEVA
Oulu 1969

Contents

Translated by
Hilkka Kontiopää
Valerie Jansen

Printed in Finland
KIRJAPAINO OSAKEYHTIÖ KALEVA
Oulu 1969

Introduction

Infant mortality that is mortality during the first year of life, has fallen dramatically in all advanced countries in the last thirty years. Neonatal mortality that is mortality during the *first few weeks* of life, has also fallen, but considerably more slowly As a result, the proportion of neonates in infant mortality has increased and now amounts to approximately two-thirds.

This trend has everywhere stimulated investigation into the etiology of neonatal mortality and efforts to reduce it.

Most deaths within the first 24 hours of life occur as a result of intrauterine or intranatal factors, as in stillbirths. Clifford states What kills a baby ten minutes before birth, is probably the same factor that kills at ten minutes after birth (28) The term *perinatal mortality* was coined to cover the mortality of the foetal period and neonatal period combined.

The perinatal mortality rate not only reflects the number of deaths during this period but should also be understood as a measure of health care, closely connected with the health of the surviving children. Nixon wrote The perinatal death rate is also an index of the number of near-deaths which may have occurred. Like an iceberg, we see only a proportion of the ill-results, the deaths. But we must not forget the submerged and larger fraction, the near-deaths and the harm which they cause. The correlation is suggestive, because some causes of death — premature delivery asphyxia during labour Rhesus incompatibility — are known to be associated with the occurrence of mental and physical defects in *some of the survivors.* With reduction in perinatal mortality there will also follow pari passu, a diminution *in perinatal* morbidity (103)

Premature, or *low birth weight infants* are the most important group *in perinatal mortality* in various surveys they comprise 50-70 per cent of this mortality Prematurity was first given attention in *1919 by Ylppö (172)* who suggested the group limit of a birth weight of 2500 grams which is still in use. Efforts have, however *been made to find* increasingly accurate criteria to *determine* the limit of risk groups versus non-risk groups, and *increasing attention is being* focused on the gestational age, as well as birth weight.

The mean birth weights of populations from different geographical districts show remarkable differences, a fact which is partly reflected in the frequency of low birth weight infants. There are also regional differences in the mean gestational length and therefore a determination and detailed analysis of risk groups in the light of these two characteristics requires basic information about each population.

Despite progress in the intensive care of the newborn, the results are as yet far from satisfactory On the other hand, obstetric help often comes too late, after the foetal death has already occurred. It would be better to give mothers of risk group infants intensified prenatal care as soon as pregnancy has started and intensive obstetric therapy in good time. The vast majority of pregnancies culminate in the birth of a healthy infant, and the problem is how to identify early in pregnancy from a large population of parturients those whose infants are likely to belong to a risk group.

Purpose of the present study

1 To analyse the variations in and correlations of birth weight and gestational age in the present series

2 To determine the correlation of perinatal mortality with birth weight and gestational age

3 To find out the possible correlations between birth weight and perinatal mortality with the mother's biological characteristics and socio-economic circumstances.

4 To study how and to what extent, the child's birth weight and risk of perinatal mortality can be predicted early in pregnancy from the mother's biological characteristics and socio-economic circumstances.

In order to identify risk-group mothers more knowledge is needed about the factors influencing birth weight and gestational age. It is known from many earlier studies that low birth weight and variations in perinatal mortality are closely connected with the mothers biological characteristics (e.g age, parity height weight general health) On the other hand, there is also known to be a correlation with the mothers social and economic circumstances, and there may equally well be a causal connection with the mothers environment (e.g rural or industrial) and the public health services available Birth weight and perinatal mortality are typical variables in human biology and can only be judged in the context of the total environment.

Purpose of the present study

1. To analyse the variations in and correlations of birth weight and gestational age in the present series.
2. To determine the correlation of perinatal mortality with birth weight and gestational age.
3. To find out the possible correlations between birth weight and perinatal mortality with the mother's biological characteristics and socio-economic circumstances.
4. To study how and to what extent, the child's birth weight and risk of perinatal mortality can be predicted early in pregnancy from the mother's biological characteristics and socio-economic circumstances.

Review of the literature

Determination of risk group criteria on the basis of the child's characteristics

In his study of 1919 Ylppo suggested a classification of prematurity based on birth weights under 2500 grams (172) This criterion indicative of abnormal immaturity was gradually accepted in general practice The American Academy of Pediatrics recommended it in 1935 and WHO in 1948 (168)

Since the early 1950s, increasing attention has been given to gestational age and birth weight combined in the determination of the child's maturity and chance of survival (27 45 67 73 77 91 129 137 141) It has clearly emerged from these studies that not all children with a birth weight under 2500 g were premature in view of gestational age. WHO recommended in 1961 that the term premature be abandoned in connection with children with a birth weight under 2500 g and replaced by the term low birth weight infant (169)

Since the child's risk of death has been related to the twin factors of birth weight and gestational age, attention has also been devoted to children whose birth weight falls outside the range of distribution considered as normal calculated separately for each gestational age group Gruenwald used standard deviations to measure this distribution (57) allotting a plus and minus score based on the standard deviation with a rating between 0— —2 for birth weights lower and 0— +2 for those higher than in normal cases (59) Lubchenco was the first, in 1963 to present the distribution of birth weights by percentiles (86) and this custom has been generally accepted (14 24 38 62 87 102, 108)

In the light of these studies it seems increasingly apparent that both the mortality (14 16 21) and morbidity (16, 30, 66 89 130, 160, 161) rates vary in children of equal weight but of different gestational age. For this reason efforts have been made to create methods of appraisal by which the degree of foetal development, i e. gestational age, can be determined with the greatest possible accuracy from the various biological characteristics of the newborn (80 94 100 152)

The mother's biological characteristics socio-economic and other environmental circumstances

There is a very extensive literature on maternal biological characteristics and socio-economic status, and on regional factors pertinent to perinatal mortality and low birth weight. Reference may be made here to an excellent general survey recently published on the factors contributing to low birth weight in the newborn (4—6)

Community studies in relation to birth weight and perinatal mortality

McKeown and Gibson carried out an investigation of 23 970 births in Birmingham in 1947 calculating perinatal mortality according to the gestational age birth weight and sex of the child and analysing the correlation of birth weight with maternal age parity and socio-economic circumstances (53—55 90—92)

Shapiro compared two parturient populations in New York in 1955—57 with regard to perinatal mortality and frequency of low birth weight, focusing his attention on the different levels of the medical care available to these groups (132, 133).

The British Perinatal Mortality Survey is the most extensive study in this field (21). It covers 16,994 births in Great Britain during one week in 1958 plus 7 117 perinatal deaths in a three month period. Information was collected on the mothers' biological characteristics and socio-economic circumstances, general health and medical care during pregnancy, obstetric help, and postmortem diagnoses of the dead infants.

In addition, there are several perinatal studies in progress, among them The North Carolina Study of Fetal and Neonatal Deaths (26), a combined project of several hospitals, with the results published in a series of publications (1—3, 36, 56, 118, 163).

Use of multi-variable analyses

The etiology of perinatal mortality and low birth weight is typically multi factorial. In the 1960s their study with the aid of multi-variable analysis has become increasingly popular (1—3, 40, 41, 56).

Review of the literature

Determination of risk group criteria on the basis of the child s characteristics

In his study of 1919 Ylppö suggested a classification of prematurity based on birth weights under 2500 grams (172) This criterion indicative of abnormal immaturity was gradually accepted in general practice The American Academy of Pediatrics recommended it in 1935 and WHO in 1948 (168)

Since the early 1950s, increasing attention has been given to gestational age and birth weight combined in the determination of the child s maturity and chance of survival (27 45 67 73 77 91 129 137 141) It has clearly emerged from these studies that not all children with a birth weight under 2500 g were premature in view of gestational age WHO recommended in 1961 that the term prematu re» be abandoned in connection with children with a birth weight under 2500 g and replaced by the term low birth weight infant (169)

Since the child s risk of death has been related to the twin factors of birth weight and gestational age attention has also been devoted to children whose birth weight falls outside the range of distribution considered as normal calculated separately for each gestational age group Gruenwald used standard deviations to measure this distribution (57) allotting a plus and minus score based on the standard deviation with a rating between 0— —2 for birth weights lower and 0— +2 for those higher than in normal cases (59) Lubchenco was the first, in 1963 to present the distribution of birth weights by percentiles (86) and this custom has been generally accepted (14 24 38 62, 87 102, 108)

In the light of these studies it seems increasingly apparent that both the mortality (14 16 21) and morbidity (16 30 66 89 130, 160 161) rates vary in children of equal weight but of different gestational age. For this reason efforts have been made to create methods of appraisal by which the degree of foetal development, i.e. gestational age can be determined with the greatest possible accuracy from the various biological characteristics of the newborn (80 94 100 152)

The mother s biological characteristics socio-economic and other environmental circumstances

There is a very extensive literature on maternal biological characteristics and socio-economic status, and on regional factors pertinent to perinatal mortality and low birth weight Reference may be made here to an excellent general survey recently published on the factors contributing to low birth weight in the newborn (4—6)

Community studies in relation to birth weight and perinatal mortality

McKeown and Gibson carried out an investigation of 23 970 births in Birmingham in 1947 calculating perinatal mortality according to the gestational age birth weight and sex of the child and analysing the correlation of birth weight with maternal age, parity and socio-economic circumstances (53—55 90—92)

review there were 66 local physicians working in the district. There were 373 obstetric beds in the district's 33 hospitals, 28 of the hospitals were *supervised* by the *local physicians*, while 5 with a total of 173 beds, were run by 7 specialized obstetricians and gynaecologists. There were 11 pediatricians in the district in that year. On_ per cent of the deliveries of the present survey occurred at home, the same percentage as for births in 1966.

Before the study proper was launched, a pilot *study was carried out in the district, and the questionnaire was designed on the* basis of the information obtained. Local mid wives were informed of the purpose of the study of how to complete the questionnaire and how to interview the patients, by means of circular letters and meetings. While the information was being collected they could get in touch with the author at any time.

The study covered all the live born and stillborn infants with birth weights of 600 grams or more

Information was available on 12,068 births. Stillbirths and infants who died before the age of 28 days totalled 316. According to the central Office of Statistics, births in this district *during 1966* totalled *12,527* of which 330 *died in the perinatal* period (159). Although the present study does not exactly cover the year *1966, the figures can be compared to see whether* information on all births was collected. The present series comprised 96.3 per cent of all births in 1966, and the present figure for perinatal deaths is 95 8 per cent of the relevant mortality in 1966. The present series had 13 fewer stillbirths, and 1 neonatal death less than was recorded by the Central Office of Statistics figures for 1966. Statistics on the frequency of *low birth* weight are kept in Finland by the National Medical Board, which collects the data from antenatal clinics and from hospitals. Live births with birth weights of 601—2500 grams in 1966 in the district of the present study totalled 540 (112) while the present series comprised 524 hence the total of low birth weight infants is 97.0 per cent of the relevant 1966 figure.

The information collected contained 163 twin births which were excluded from the study There were 11 905 *single births. Table* 1 shows these distributed into *low birth weight infants* with a birth weight under 2500 g, and those with birth weights of or exceeding 2500 g, giving the mortality rates of the different phases of the perinatal period per group. All infants of a gestational age between the beginning of the 38th and the end of the 42nd gestational week have been considered *as term births. Pre-term births* were taken

TABLE 1 *Distribution of the present series of cases by low birth weight and by perinatal mortality*

Mortality during perinatal period	Birth weight 2500 g or more		Birth weight less than 2500 g		Total	
	Number of cases	Rate per thousand	Number of cases	Rate per thousand	Number of cases	Rate per thousand
Stillbirths	70	6.1	90	180.4	160	13 44
Died at 0—7 day	39	3.4	69	138.3	108	9.07
Died at 8—28 days	10	0.9	5	10.0	15	1.26
Total mortality	119	10.4	164	328.7	283	23.77
Al_ at the end of perinatal period	11,287	989.6	335	671.3	11,622	976.23
Total	11 406	1000.0	499	1000.0	11 905	1000.00

Material and method

The material comprised all the births in the provinces of Oulu and Lapland — the most northerly parts of Finland — over one year These provinces cover 160 000 sq km., which is about 48 per cent of the total area of the country The population is roughly 604 000 of whom some 204 000 are urban dwellers. The majority of the population are Finns though there are also some 3,500 Lapps. The district is situated at 63°30 —70°0' North and 21°0'—30°31 East. The mean temperature in January is —12°C below zero and in July +15°C. Daylight in December averages 2 hours and in June 23 hours per day Fig 1 shows the area from which the data were collected

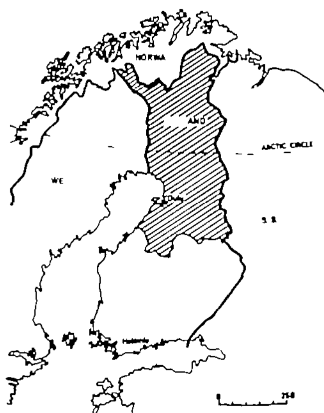


Fig 1 Area from which the data were collected

Since the study was prospective, inclusion in the survey was determined by the calculated term the series comprised all the mothers in this district with calculated term falling between January 1—December 31 1966 A small percentage of the births in fact occurred towards the end of 1965 and early in 1967 The calculated term as is customary was counted from the first day of the last menstrual period Where this date was unknown the expected term was estimated from the date of commencement of foetal movements and progress of the pregnancy

Information on the mothers was collected by the antenatal clinics on a questionnaire. The data used for the study are presented in Appendix I Efforts were made to obtain this information in the 24th to 28th gestational week but where this failed the questionnaire was completed later in the pregnancy or after the delivery Information on the child's date of birth birth weight, death, illness, etc., is forwarded by maternity homes to the antenatal clinics which enter it on their files. Information on the child up to the age of 28 days was obtained at the mother's follow up examination in maternity clinics.

The data was collected at the 157 antenatal clinics of the district by the 188 local midwives who have a two-year period of training and work under the local urban and rural physicians who also take part in antenatal clinic work Legislation providing for the setting up of antenatal and child clinics by local authorities has been in operation in Finland since 1944 The local authorities are under a legal obligation to arrange free examinations at the clinics for pregnant mothers and their newborn children In the year under

in a group length of gestation unknown No other criteria were used to determine the gestational weeks. The expected date determined by the antenatal clinics was not corrected with the exception of a few cases in which a check was made to make sure that the dates had been correctly written.

Information on the child up to the age of 28 days was nearly always easy to obtain Those moving from the district were traced either by the network of antenatal clinics or by social welfare authorities. In only five cases was the child lost sight of after the first week of life.

In the analysis of the data, the following groups were used: (1) perinatal deaths, (2) birth weight under 2500 g, (3) gestation of 37 weeks or less, and (4) gestation of 43 weeks or more. A pseudo-random computer sample of 1,000 cases was taken of the total of 9 974 cases (Table 2) of term infants living at the end of the perinatal period and those of unknown gestational age the sample was based on the serial numbers printed on the questionnaires. This group of 1,000 will be termed *controls* Whenever results were to demonstrate the distribution of the total material the correction coefficient (inverse number of the sampling ratio), to avoid decimals, was 10 instead of 9 974 which is of no importance in the results. The number of cases in the total series, therefore, is given as 11 931 instead of 11 905

The data on mothers were entered on the questionnaires of 92 per cent of the cases prior to delivery A study of the completion of questionnaires for low birth weight infants, dead infants and controls revealed differences between the groups. The questionnaires for dead infants with birth weights of 2500 g or more were completed almost as often before birth as those for the controls, whereas those for low birth weight infants were more often completed after birth, especially among the dead infants of this group (29 9 per cent)

When the questionnaires were analysed for absence of individual data, it was again found that the data for the controls were most complete and those for the dead low birth weight infants least complete. The figures below show the number of questions that had a given percentage of answers missing in the two groups.

	Less than 5 per cent	5.1—10 per cent	10.1—15 per cent	Total questions
Controls	36	10	1	47
Low birth weight, deaths	25	14	8	47

The questions concerning the mother's age, marital status, parity abortions and place of residence were answered on practically all forms (answers were missing on less than 0 8 per cent of questions). For deaths and low birth weight infants, missing information was later traced from antenatal clinic records concerning previous low birth weight infants and previous perinatal deaths. For this reason the information is less complete on this point in the control group thus no reply was given to the former question in 10.7 per cent and to the latter in 7 1 per cent, as against 3.7 and 2.4 per cent for the perinatal deaths of low birth weight infants. For questions on deaths and low birth weight infants that were initially not answered and later answered from clinic records and otherwise, it appeared that questions requiring a negative answer had been answered less often than those requiring a positive answer

All calculations were made by computer The variation of the birth weight and gestational age, and the relationship of perinatal mortality to them were calculated by the customary statistical methods. The other two questions studied correlation of perinatal mortality and birth weight with the mother's biological characteristics and socio-economic circumstances, and the prediction of perinatal mortality and birth weight from the biological characteristics and socio-economic circumstances at the beginning of pregnancy were combined, Fisher's discriminant function analysis being used in the calculation (44). The purpose of the analysis was to find the linear

TABLE 2. *Distribution of survivals at the end of perinatal period into pre term term and post term births Low birth weight infants and those with birth weights of 2500 g or more are shown separately*

Birth weight g	Gestation 37 weeks or less	Gestation 38—4 weeks	Gestation 43 weeks or more	Length of gestation not known	Total
2500 g or more	696	9 615	617	359	11,287
Less than 2500 g	191	121	6	17	335
Total	887	9,736	623	376	11 622

TABLE 3 *Distribution of perinatal deaths into pre term term and post term births Low birth weight infants and those with birth weights of 2500 g or more are shown separately Mortality rates per thousand are calculated from the relevant distributions of the total number of cases*

Birth weight g	Gestation 37 weeks or less	Gestation 38—42 weeks	Gestation 43 weeks or more	Length of gestation not known	Total
2500 g or more					
— number	25	79	11	4	119
— mortality per thousand	34.7	8 1	17.5	11.0	10.43
Less than 2500 g					
— number	123	25	2	14	164
— mortality per thousand	391.7	171.2	250.0	451.6	328.66
Total					
— number	148	104	13	18	283
— mortality per thousand	143 0	10.7	20.4	45.6	23.77

as those prior to the beginning of the 38th gestational week and *post term* those whose 43rd week had commenced. The gestational age is indicated in terms of weeks that had begun For example, the 40th week refers to 274—280 days calculated from the first day of last menstrual period Table 2 gives the distribution of the 11 622 survivals at the end of the perinatal period by gestational age into pre-term term and post term infants, and those of unknown gestational age Table 3 gives the corresponding figures for the 283 infants who died in the perinatal period with mortality rates.

Since inclusion in the present survey was decided at the antenatal clinic, the length of gestation was calculated according to the calculated term and the actual date of the child's birth. In a large number of cases the calculated term was determined by a method which in some months of the year made the expected date 1—3 days late Should pregnancies start uniformly on the different days of the year the expected date of delivery calculated by this method would be on average 0 76 days late

Birth weight was recorded on the questionnaire in the usual way within 5 grams either way whereas truncated 100 gram class limits were used in all calculations For example weight group 1500 g comprised birth weights of 1500—1599 grams.

The birth weight was known in every case Cases in which the expected date of delivery could not be determined according to the first day of the last menstrual period were placed

The calculations for discriminant function analysis were carried out with an Elliott 803 computer Group dispersions, group means, group covariances and group correlations of the variables were calculated. The pooled covariance matrix of the groups was calculated, the characteristic equation was solved and the eigenvector for each pair of groups to be discriminated was determined (32) The significance of the individual discriminant functions was studied by means of Rao's chi square approximation (116). The next step was to calculate the correlations of the discriminant, group means and group dispersions.

Lastly a classification to decide the group membership of each individual was calculated by means of the parameters already obtained, and they gave the discriminant score and probability for each case. The discriminant scores indicate the point of each case in discrimination space. The probability of membership in either of the two groups was calculated according to the distances between the point the case had obtained in discrimination space and density of the groups (32, 81) Since the figures involved were calculated from the mothers characteristics, the probability of a mother being in a particular group indicated the extent to which the relevant mother's characteristics corresponded to the typical characteristics of the group Any cases in which the variables used are known can be classified by this method, as well as the cases involved in the present analysis. In the present study the total number of cases was classified on the basis of the probability classification of analysis A The true low birth weight rates were used as a criterion to measure the effectiveness of the above probability classification.

According to the result of the classification, the present data were divided into identifiable risk groups of varying degree, and the characteristics of the infant and mother in these groups were studied.

multi variable combination which best discriminates the studied risk groups from control group and on this basis to form a function for classification to help define for individual cases the probability that they belong to a particular group

The object of the study was to pick out those mothers whose pregnancy ran a risk of perinatal mortality or low birth weight. The hypothesis was moreover that perinatal deaths do not form a uniform group but that the low birth weight deaths make up a group different from those with birth weight of 2500 g or more for this reason the discriminant analysis was carried out with 3 pairs of groups Every analysis involved 2 groups, one consisting of 1000 control cases while the other represented a *risk group* The risk group was selected as follows

Analysis	Risk group	Number of cases in risk group
A	Birth weight less than 2500 g, all cases	499
B	Birth weight less than 2500 g, deaths only	164
C	Birth weight 2500 g or more, deaths only	119

The risk group of analysis A thus contained that of analysis B which was one-third of the former

Since the discrimination score obtained by the analysis is a linear combination of the variables used the effect of individual variables in the discrimination depends on the other variables used and in another context the effect of the variables might be different For this reason the pairs of groups used in analyses A and B were also analysed with a different combination of variables. The analyses A B and C had 43 variables, the same in all these analyses. The groups of analysis A 1 were those of analysis A and the groups of analysis B 1 those of analysis B, but the number of variables in A 1 and B 1 was 27 of which 23 were also involved in analyses A and B Appendix 1 presents the variables of the multiple discriminant analysis and Table 10 shows (see page 23) the variables used in each analysis

All variables were characteristic of the mothers and their sphere of life and none of them concerned the course of the pregnancy the delivery or the child born Analyses A 1 and B 1 included however two variables which measured attitudes during pregnancy The variables were classified according to their information content, and the classification is presented below even though the class limits were often approximate and a short definition of all information content was difficult

Classification	*Variables*
Biological characteristics	1—8
Socio economic circumstances	9—47
Social standing	9—16
Conditions in childhood	17—20
School attendance and intellectual interest	21—22
Attitudes to pregnancy and to help by public authorities	23—25
Smoking	26
Working	27—33
Housing standards	34—37
Standard of living	38—39
Internal migration, and particulars of the current and possible earlier place of residence	40—47

The mathematical theory on which the multiple discriminant analysis is based presupposes that the variables used are continuous and normally distributed *Not all the variables present fulfilled these conditions.* The influence of such variables on a discriminant analysis is not known in detail

Since information on every variable was not available for all the cases, a correction programme was used for the analyses the missing observation was replaced by a random value according to the distribution of the relevant variable in each group The missing observations for control cases were corrected according to the distribution of the controls, those for the low birth weight cases according to that of the low birth weight infants, etc

The calculations for discriminant function analysis were carried out with an Elliott 803 computer Group dispersions, group means, group covariances and group correlations of the variables were calculated. The pooled covariance matrix of the groups was calculated, the characteristic equation was solved and the eigenvector for each pair of groups to be discriminated was determined (32). The significance of the individual discriminant functions was studied by means of Rao's chi square approximation (116). The next step was to calculate the correlations of the discriminant, group means and group dispersions.

Lastly a classification to decide the group membership of each individual was calculated by means of the parameters already obtained, and they gave the discriminant score and probability for each case. The discriminant scores indicate the point of each case in discrimination space. The probability of membership in either of the two groups was calculated according to the distances between the point the case had obtained in discrimination space and density of the groups (32, 81) Since the figures involved were calculated from the mothers characteristics, the probability of a mother being in a particular group indicated the extent to which the relevant mother's characteristics corresponded to the typical characteristics of the group. Any cases in which the variables used are known can be classified by this method, as well as the cases involved in the present analysis. In the present study the total number of cases was classified on the basis of the probability classification of analysis A. The true low birth weight rates were used as a criterion to measure the effectiveness of the above probability classification.

According to the result of the classification, the present data were divided into identifiable risk groups of varying degree, and the characteristics of the infant and mother in these groups were studied.

multi variable combination which best discriminates the studied risk groups from control group and on this basis to form a function for classification to help define for individual cases the probability that they belong to a particular group

The object of the study was to pick out those mothers whose pregnancy ran a risk of perinatal mortality or low birth weight. The hypothesis was, moreover that perinatal deaths do not form a uniform group but that the low birth weight deaths make up a group different from those with birth weight of 2500 g or more for this reason the discriminant analysis was carried out with 3 pairs of groups Every analysis involved 2 groups one consisting of 1000 *control cases* while the other represented a *risk group* The risk group was selected as follows

Analysis	Risk group	Number of cases in risk group
A	Birth weight less than 2500 g, all cases	499
B	Birth weight less than 2500 g, deaths only	164
C	Birth weight 2500 g or more, deaths only	119

The risk group of analysis A thus contained that of analysis B which was one-third of the former

Since the discrimination score obtained by the analysis is a linear combination of the variables used, the effect of individual variables in the discrimination depends on the other variables used and in another context the effect of the variables might be different. For this reason the pairs of groups used in analyses A and B were also analysed with a different combination of variables. The analyses A B and C had 43 variables, the same in all these analyses. The groups of analysis A 1 were those of analysis A and the groups of analysis B 1 those of analysis B but the number of variables in A 1 and B 1 was 27 of which 23 were also involved in analyses A and B Appendix 1 presents the variables of the multiple discriminant analysis, and Table 10 shows (see page 23) the variables used in each analysis.

All variables were characteristic of the mothers and their sphere of life and none of them concerned the course of the pregnancy the delivery or the child born Analyses A 1 and B 1 included however two variables which measured attitudes during pregnancy The variables were classified according to their information content, and the classification is presented below even though the class limits were often approximate and a short definition of all information content was difficult.

Classification		*Variables*
Biological characteristics		1—8
Socio economic circumstances		9—47
Social standing	9—16	
Conditions in childhood	17—20	
School attendance and intellectual interest	21—22	
Attitudes to pregnancy and to help by public authorities	23—25	
Smoking	26	
Working	27—33	
Housing standards	34—37	
Standard of living	38—39	
Internal migration and particulars of the current and possible earlier place of residence	40—47	

The mathematical theory on which the multiple discriminant analysis is based presupposes that the variables used are continuous and normally distributed. Not all the variables present fulfilled these conditions The influence of such variables on a discriminant analysis is not known in detail

Since information on every variable was not available for all the cases, a correction programme was used for the analyses the missing observation was replaced by a random value according to the distribution of the relevant variable in each group The missing observations for control cases were corrected according to the distribution of the controls, those for the low birth weight cases according to that of the low birth weight infants, etc

The calculations for discriminant function analysis were carried out with an Elliott 803 computer. Group dispersions, group means, group covariances and group correlations of the variables were calculated. The pooled covariance matrix of the groups was calculated, the characteristic equation was solved and the eigenvector for each pair of groups to be discriminated was determined (32). The significance of the individual discriminant functions was studied by means of *Rao's* chi square approximation (116). The next step was to calculate the correlations of the discriminant, group means and group dispersions.

Lastly a classification to decide the group membership of each individual was calculated by means of the parameters already obtained, and they gave the discriminant score and probability for each case. The discriminant scores indicate the point of each case in discrimination space. The probability of membership in either of the two groups was calculated according to the distances between the point the case had obtained in discrimination space and density of the groups (32, 81). Since the figures involved were calculated from the mothers' characteristics, the probability of a mother being in a particular group indicated the extent to which the relevant mother's characteristics corresponded to the typical characteristics of the group. Any cases in which the variables used are known can be classified by this method, as well as the cases involved in the present analysis. In the present study the total number of cases was classified on the basis of the probability classification of analysis A. The true low birth weight rates were used as a criterion to measure the effectiveness of the above probability classification.

According to the result of the classification the present data were divided into identifiable risk groups of varying degree, and the characteristics of the infant and mother in these groups were studied.

Results

1 Variations in and correlations of birth weight and gestational age

The series comprised 32.7 per cent primi paras, 24 1 per cent parity 2 14.3 per cent parity 3 10.5 per cent parity 4 and 18 4 per cent parity 5 or more
Of the infants born whose sex was indicated 6 195 (52 1 per cent) were boys and 5,702 (47 9 per cent) girls, which gave a sex ratio of 1086 boys per 1000 girls In 34 instances the sex was not indicated. The arithmetic means and standard deviations of birth weight length at birth and gestational age were as follows

	Girls	Boys	Total
Birth weight, g			
Mean	3382	3500	3444
S.d.	539	590	569
Length at birth cm			
Mean	49 9	50.5	50.2
S.d.	2.3	2.6	2.5
Gestational age, days			
Mean	278.0	276.9	277 4
S d.	15.0	15 0	14 9

The birth weight and gestational age of all cases are cross-indexed in Table 27 (Appendix 2) in class intervals of 100 g weight and 1 week. Fig. 2 shows the distribution of birth weights by 100 gram weight groups. The most common weight group is 3600 grams (8 4 per cent) and 25 0 per cent fall within the range of 3500—3799 grams

Mean birth weights per gestational week were expressed both by the arithmetic means and medians and intrauterine growth curves were plotted for both. The 10th 25th, 50th, 75th and 90th percentiles are presented in Tables 4 and 5 The smoothed values were calculated using polynomial regression of degree 3 The median values up to the 34th gestational week were slightly lower and after the 34th week slightly higher than the arith metic means of the birth weights. The 10th and 90th percentile curves calculated by different methods agree fairly well from the 34th gestational week onwards. For the pur pose of the comparisons in the present study

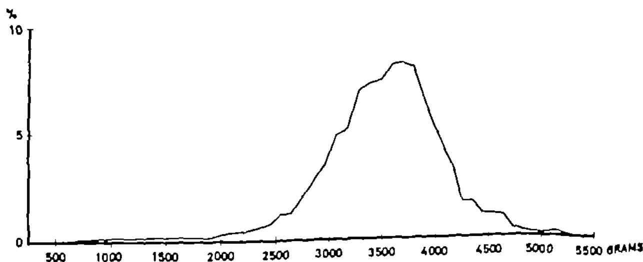


Fig. 2 Percentage distribution of the total number of cases int 100 gram weight group

TABLE 4 *Mean values of birth weights in the 25th—46th weeks of gestation and the percentile values calculated from them. Total series of cases*

Gestation, weeks	Number of cases	Mean	Smoothed values				
		g	10 %	25 %	50 %	75 %	90 %
25	6	900	450	700	955	1190	1410
26	11	1150	460	730	1050	1360	1635
27	12	1120	490	810	1180	1540	1860
28	13	1230	570	930	1340	1730	2095
29	13	1510	690	1080	1510	1940	2330
30	26	1550	850	1250	1700	2150	2555
31	30	1760	1030	1450	1910	2360	2780
32	24	2250	1240	1660	2120	2580	2990
33	65	2540	1460	1875	2330	2785	3200
34	77	2600	1690	2100	2540	2990	3390
35	149	2530	1925	2320	2750	3180	3570
36	229	2900	2150	2530	2945	3360	3735
37	380	3080	2370	2730	3125	3520	3880
38	777	3240	2570	2910	3290	3660	4000
39	1656	3390	2750	3070	3420	3780	4100
40	3050	3460	2900	3200	3530	3870	4170
41	2725	3610	3010	3300	3610	3930	4220
42	1657	3720	3070	3350	3650	3950	4230
43	470	3690	3090	3360	3650	3940	4210
44	103	3550	3050	3315	3600	3890	4150
45	40	3530	2945	3215	3500	3790	4060
46	22	3440	2770	3050	3340	3650	3930
all weeks	11,931	3440					

TABLE 5 *Median values of birth weights in the 25th—46th weeks of gestation and the percentile values calculated from them. Total series of cases.*

Gestation, weeks	Number of cases	Median	Smoothed values				
		g	10 %	25 %	50 %	75 %	90 %
25	6	800	720	750	780	960	1760
26	11	975	740	820	920	1175	1955
27	12	900	740	880	1070	1400	2150
28	13	1230	765	980	1230	1630	2350
29	13	1375	855	1120	1450	1860	2550
30	26	1317	990	1280	1660	2100	2750
31	30	1720	1150	1480	1875	2340	2950
32	24	2100	1340	1690	2100	2570	3140
33	65	2617	1550	1910	2320	2800	3320
34	77	2623	1780	2140	2540	3010	3490
35	149	2846	2010	2360	2760	3210	3650
36	229	2969	2230	2580	2960	3400	3790
37	380	3132	2450	2790	3150	3570	3920
38	777	3243	2650	2980	3310	3710	4030
39	1656	3424	2830	3140	3455	3830	4120
40	3050	3530	2970	3270	3570	3920	4180
41	2725	3628	3080	3360	3650	3970	[illegible]
42	1657	3763	3140	3410	3700	4000	[illegible]
43	470	3718	3150	3405	3710	[illegible]	[illegible]
44	103	3594	3105	3345	3675	[illegible]	4155
45	40	3600	2990	3220	3580	[illegible]	[illegible]
46	22	3620	2800	3030	3440	[illegible]	[illegible]
all weeks	11,931	3530					

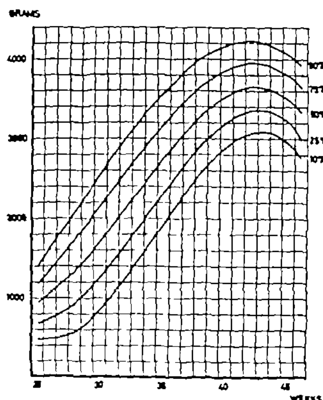


Fig 3 Intrauterine weight gain curves of the total number of cases, giving different percentiles calculated from the arithmetic mean of birth weights in the 25th—46th gestational weeks

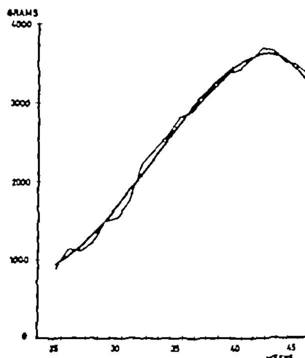


Fig 4 The 50th percentile intrauterine growth curve of the total number of cases calculated from mean values of birth weight One curve plotted from the unsmoothed means and another smoothed with polynomial regression of degree 3 in the 25th—46th gestational weeks

it therefore made little difference which of the two uterine growth curves obtained was used and the value based on the mean was chosen The percentile graphs based on the calculation of mean values is shown in Fig 3 while Fig 4 gives the 50th percentile curve plotted according to unsmoothed mean values together with a smoothed curve.

Since the number of cases for earlier gestational weeks was small when the growth of boys and girls was studied separately two weeks were combined The results are presented in Table 6 The table reveals that, in the present survey the mean birth weight of boys was consistently higher than that of girls from the 33rd to 34th gestational weeks onwards.

TABLE 6 *Mean values of girls and boys birth weights by weeks of gestation*

Gestation weeks	Girls		Boys	
	Number	Birth weight, g	Number	Birth weight, g
25—26	9	1133	8	975
27—28	11	1136	13	1254
29—30	15	1551	24	1525
31—32	26	2088	28	1882
33—34	67	2537	75	2604
35—36	169	2813	208	2927
37—38	500	3084	657	3260
39—40	2128	3380	2558	3486
41—42	2224	3561	2148	3735
43—44	297	3577	275	3756

2 Perinatal mortality rate correlated with birth weight and gestational age

Table 28 (Appendix 3) shows the perinatal deaths cross indexed according to birth weight and gestational age in class intervals of 100 g weight and 1 week. The perinatal deaths totalled 83 159 (56.6 per cent) were boys and 122 (43.4 per cent) girls, while the sex of two was not indicated. The table also gives the perinatal mortality rates per thousand for the total number of cases by birth weight and gestational age group. Mortality rates clearly fell to a minimum in the weight range of 3500-3999 grams, and did not rise very steeply even towards the highest birth weight classes, but since the number of cases was so limited a detailed analysis was difficult. For the low birth weight infants, the first steep fall of about 50 per cent was seen in the weight range of 1800-1900 grams, and another fall of the same order in that of 2400—2500 grams that is to say the class limit separating the low birth weight group. Mortality rates per 200 gram weight groups are illustrated by the graphs of Fig. 5 In order to avoid combining the biggest birth weight group of the low birth weight infants with the 2500—2599 gram group, the weight range 600—899 was nevertheless combined. In Fig. 5 the lowest mortality rate, 3.5 per thousand, was in the 3500—3699 gram range, but if the groups had been differently combined the mortality rate would be equally low in the 3800—3999 gram range.

Table 8 also shows that mortality rates calculated according to the gestational week are at their lowest in the 40th week of gestation. Pre-term births exhibit a roughly 50 per cent fall in mortality from the 31st to the 32nd week and again from the 36th to the 37th week. Fig. 6 presents mortality rates according to gestational age by fortnightly periods. The pre-term group limit of the beginning of the 38th week does not coincide with a steep fall, whereas mortality increases



Fig 5 Perinatal mortality by 200 gram birth weight groups.

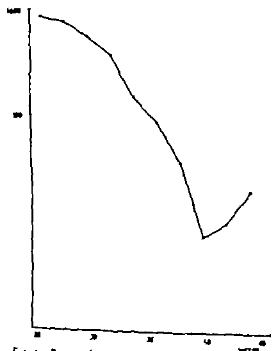


Fig. 6. Perinatal mortality by week of gestation. The rates are calculated for fortnightly period

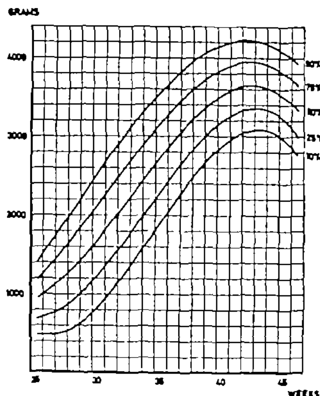


Fig 3 Intr terine weight gain curves of the total number of cases giving different percentiles calculat d from the arithmetic mean of birth weights n the 25th—46th gestational weeks.

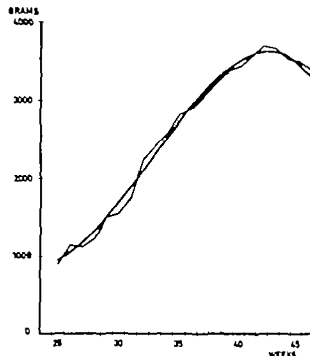


Fig 4 The 50th percentile int auterine growth curve of the total number of cases, calculat d from mean values of bi th weight One curve plotted from the unsmoothed means and another smoothed w th polynomial regression of degree 3 in the 25th—46th gestat onal weeks

it therefore made little difference which of the two uterine growth curves obtained was used and the value based on the mean was chosen The percentile graphs based on the calculation of mean values is shown in Fig 3 while Fig 4 gives the 50th percentile curve plotted according to unsmoothed mean values together with a smoothed curve

Since the number of cases for earlier gestational weeks was small when the growth of boys and girls was studied separately two weeks were combined The results are presented in Table 6 The table reveals that, in the present survey the mean birth weight of boys was consistently higher than that of girls from the 33rd to 34th gestational weeks onwards.

TABLE 6 *Mean values of girls' and boys birth weights by weeks of gestation*

Gestation, weeks	Girls		Boys	
	N mbe	B rth weight g	Number	B rth weight, g
25—26	9	1133	8	975
27—28	11	1136	13	1254
29—30	15	1553	24	1525
31—32	26	2088	28	1882
33—34	67	2537	75	2604
35—36	169	2813	208	2927
37—38	500	3084	657	3260
39—40	2128	3380	2358	3486
41—42	2224	3561	2148	3733
43—44	297	3577	275	3756

2. Perinatal mortality rate correlated with birth weight and gestational age

Table 28 (Appendix 3) shows the perinatal deaths cross-indexed according to birth weight and gestational age in class intervals of 100 g weight and 1 week. The perinatal deaths totalled 283 159 (56.6 per cent) were boys and 122 (43 4 per cent) girls, while the sex of two was not indicated. The table also gives the perinatal mortality rates per thousand for the total number of cases by birth weight and gestational age group Mortality rates clearly fell to a minimum in the weight range of 3500-3999 grams, and did not rise very steeply even towards the highest birth weight classes but since the number of cases was so limited a detailed analysis was difficult. For the low birth weight infants, the first steep fall of about 50 per cent was seen in the weight range of 1800-1900 grams, and another fall of the same order in that of 2400—2500 grams, that is to say the class limit separating the low birth weight group. Mortality rates per 200 gram weight groups are illustrated by the graphs of Fig. 5 In order to avoid combining the biggest birth weight group of the low birth weight infants with the 2500—2599 gram group, the weight range 600—899 was nevertheless combined. In Fig. 5 the lowest mortality rate, 3.5 per thousand, was in the 3500—3699 gram range, but if the groups had been differently combined the mortality rate would be equally low in the 3800—3999 gram range.

Table 28 also shows that mortality rates calculated according to the gestational week are at their lowest in the 40th week of gestation. Pre-term births exhibit a roughly 50 per cent fall in mortality from the 31st to the 32nd week and again from the 36th to the 37th week. Fig. 6 presents mortality rates according to gestational age by fortnightly periods. The pre-term group limit of the beginning of the 38th week does not coincide with a steep fall, whereas mortality increases



Fig. 5. Perinatal mortality by 200 gram birth weight groups.

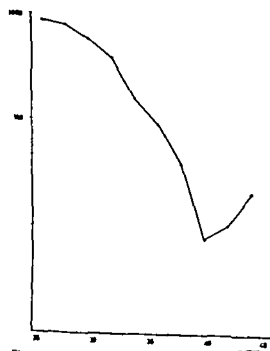


Fig. 6. Perinatal mortality by week of gestation. The rates are calculated for fortnightly periods.

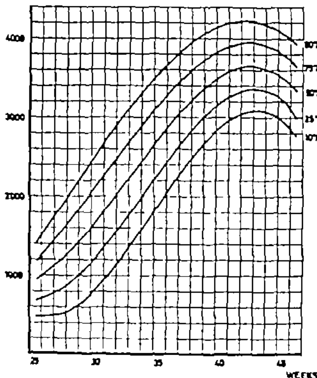


Fig 3 Intrauterine weight gain curves of the total number of cases, giving different percentiles calculated from the arithmetic mean of birth weights in the 25th—46th gestational weeks.

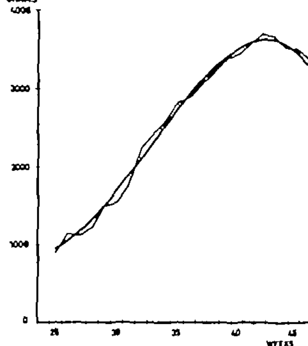


Fig 4 The 50th percentile intrauterine growth curve of the total number of cases calculated from mean values of birth weight One curve plotted from the unsmoothed means and another smoothed with polynomial regression of degree 3 in the 25th—46th gestational weeks

it therefore made little difference which of the two uterine growth curves obtained was used and the value based on the mean was chosen The percentile graphs based on the calculation of mean values is shown in Fig 3 while Fig 4 gives the 50th percentile curve plotted according to unsmoothed mean values together with a smoothed curve

Since the number of cases for earlier gestational weeks was small when the growth of boys and girls was studied separately two weeks were combined The results are presented in Table 6 The table reveals that in the present survey the mean birth weight of boys was consistently higher than that of girls from the 33rd to 34th gestational weeks onwards.

TABLE 6 *Mean values of girls' and boys birth weights by weeks of gestation*

Gestation, week	Girls		Boys	
	Number	Birth weight, g	Number	Birth weight, g
25—26	9	1133	8	975
27—28	11	1136	13	1254
29—30	15	1553	24	1525
31—32	26	2088	28	1882
33—34	67	2537	75	2604
35—36	169	2813	208	2927
37—38	500	3084	657	3260
39—40	2128	3380	2558	3486
41—42	2224	3561	2148	3735
43—44	297	3577	275	3756

TABLE 9 *Comparison of the birth weights of infants of different gestational ages by groups. 1 those who died before the beginning of delivery 2 those who died during delivery or the neonatal period and 3 those who were living at the end of the perinatal period The differences of the means of the birth weights were tested by Student's t test*

(*=P<0.05, P<0.01)

Gestation, weeks	1 Deaths before beginning of delivery		2. Deaths during delivery and neonatal period		3 Survivals at the end of perinatal period		t calculated for differences of mean birth weights of Groups 1 and 2	calculated for differences of mean birth weights of Groups 2 and 3
	Number of cases	Mean birth weight g	Number of cases	Mean birth weight g	Number of cases	Mean birth weight g		
25—26	2	1,500	12	875	3	1,500	—	2.90
27—29	10	989	16	1 143	12	1,733	0.72	2.65
30—3	12	1,325	24	1 462	44	2,188	0.97	4.54
33—35	18	1,683	18	2,177	255	2,812	2.31	4.25
36—38	31	2,136	29	2,635	1,326	3 169	2.23	4.98
39—41	21	2,866	41	3,014	7,369	3,502	0.81	6.97*
42—44	10	3,359	20	3,259	2,200	3,709	0.35	3 96
More than 44 weeks, or unknown	10	1,659	9	1 933	439	3,304	0.59	8.04
Total	114	2,085	169	2,285	11,648	3 474	1.64	28.97*

cases and separately for 8 gestational age groups. The results are presented in Table 9

A comparison of the mean birth weights of group 1 with those of group 2 revealed that the weights of the former in the 33rd to 38th week of gestation were statistically significantly lower In the other weeks of gestation the difference was not significant. When the birth weights of group 2 were compared with those of group 3 the birth weights of the surviving infants were found to be higher and the differences to be markedly larger than in the former comparison. They were statistically significant for every week of gestation. Summarizing, it may be said that the *birth weights of infants who died during the perinatal period were significantly lower than those of infants of the same gestational age who survived* and that the birth weights of infants who died before the beginning of labour were slightly lower than those of the infants who died later during the perinatal period.

Fig. 7 presents a graph of the 50th percentile of the intrauterine growth curve, with values

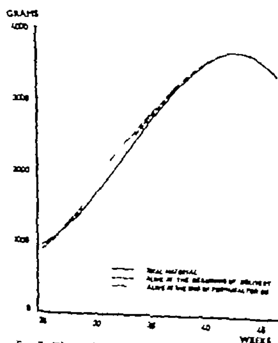


Fig. 7 The 50th percentile values of the intrauterine growth curve calculated on the total number of cases, on the infants alive at the beginning of delivery and on those alive at the end of the perinatal period.

TABLE 7 *Distribution of the cases into zones limited by the percentiles of intrauterine growth curves Pre term term and post term infants and their relevant perinatal mortality rates are listed separately*

Gestation weeks	Over 90 percentiles			50—90 percentiles			10—50 percentiles			Under 10 percentiles			Total		
	No. of deaths	Total	Mortality per thousand	No. of deaths	Total	Mortality per thousand	No. of deaths	Total	Mortality per thousand	No. of deaths	Total	Mortality per thousand	No. of deaths	Total	Mortality per thousand
37 weeks or less	6	104	57.7	17	369	46.1	83	466	178 1	42	96	437.5	148	1,035	143.0
38—42 weeks	4	794	5.0	20	3,820	5.2	31	4 411	7 0	49	840	58.3	104	9,865	10 6
43 weeks or more	1	83	12.0	3	244	12.3	3	241	12.4	6	68	88.2	13	636	20.5
Total	11	981	11.2	40	4 433	9.0	117	5 118	22.9	97	1,004	96.6	265	11,536	23.0

by roughly 100 per cent at the post term class limit of the end of the 42nd week

Table 7 presents the mortality by gestational age and the various percentiles of the intrauterine growth curve. An analysis of the overall results of this classification revealed that the mortality rate was lowest between the 50th and 90th percentiles In the over 90 percentile range the mortality rate was slightly higher but the difference was not statistically significant and was only present in pre-term infants. From the 10th to 50th percentile the mortality rate was more than twice that of over 50 Under the 10th percentile the rate was more than four times that of the 50—10 percentile range. According to gestational age the mortality rate for pre-term infants was about 14 times that of term births while the rate for post term infants was twice that of the term births

The majority of the cases in the early gestational weeks were perinatal deaths moreover 160 of the 283 deaths were still births (Table 1) For this reason the birth weights of the infants who died at different phases of the perinatal period were compared with those of the survivors Table 8 analyses the 160 stillbirths according to whether death occurred before birth or during delivery separately for the low birth weight infants and those with birth weights of 2500 g or more

TABLE 8 *Stillbirths classified into deaths before the beginning of delivery and those during delivery*

Birth weight	≥ 2500 g	<2500 g	Total	Per cent
Deaths before beginning of delivery	35	68	103	64 4
Deaths during delivery	29	17	46	28.7
Time of death unknown	6	5	11	6.9
Total	70	90	160	100.0

The birth weights of the following groups were compared Group 1 deaths before the beginning of delivery (11 stillbirths of unknown time of death were included in this group) Group 2 deaths during delivery or the neonatal period, and Group 3 survivals at the end of the perinatal period This classification was imposed on the total number of

TABLE 10. *Eigenvectors of discriminant function analyses A A1 B B1 and C Weightings of the variables have been scaled and normalized A + sign on the top of a vector indicates that positive values of weightings of variables of this vector are associated with the risk group a — sign indicates that negative values of the weightings are associated with the risk group*

	A	A1	B	B1	C
	+	—	—	+	—
1 Maternal age	-0.30701	0.28471	0.18095	-0.24452	0.53295
2. Maternal height	-0.13111	0.12539	0.09841	-0.11054	0.29192
3 Maternal weight	-0.29079	0.34209	-0.01458	-0.04623	-0.08103
4 Menarche age	-0.06048	0.07505	0.00682	-0.03301	0.08721
5 Parity	-0.11849	0.41418	-0.14531	-0.33161	0.22475
6. Number of previous abortions	0.13198	-0.18172	-0.18746	0.28420	0.02541
7 Previous low birth weight infants	0.54215	-0.58377	-0.36803	0.50229	-0.02436
8. Previous perinatal mortality	0.00991	-0.06371	-0.02300	0.12671	0.02359
9 Mother's marital status	0.28681	-0.33745	-0.19687	0.26361	0.05336
10. Mother occupation	0.12150	0.11143	-0.10814	-0.12531	0.01668
11 Father' occupation	0.07727	-0.13952	-0.03998	0.07613	-0.10335
12 Is the father farmer	0.05262	0.06373	0.15182	-0.13532	-0.00031
13 Mother sector of economy	0.08473	—	-0.08506	—	-0.14689
14 Father sector of economy	-0.10100	—	0.11872	—	-0.11108
15. Mother vocational standing	-0.04488	-0.12547	-0.10638	0.23207	0.02211
16 Father ocational standing	—	0.02525	—	-0.02541	—
17 Occupation of mother father	0.03670	—	-0.10266	—	0.07279
18 Was mother father farmer	-0.03561	—	0.05089	—	0.11866
19 Number of mother siblings	-0.06419	—	-0.06302	—	0.22745
20 Number of mother deceased siblings	0.03518	-0.03684	-0.09103	0.11038	-0.16221
21 Mother school attendance	-0.01418	0.05838	0.06397	-0.12498	0.17217
22 Intellectual interest in housekeeping and public health facilities	0.00453	-0.15381	-0.07437	0.22276	0.03307
23. Was the pregnancy wanted or not	—	-0.06685	—	-0.01100	—
24 Mother frame of mind during pregnancy	0.08396	-0.01370	-0.06293	0.05093	0.04839
25 Mother's attitude towards support by public authorities	—	0.02679	—	0.03491	—
26 Mother smoking	0.20727	—	-0.12121	—	0.14322
27 Mother attitude to strenuousness of work	—	-0.02265	—	-0.03394	—
28. Mother gainful employment	-0.02363	-0.01734	0.02219	0.06952	0.13145
29 Posture at work	-0.04325	—	0.09389	—	0.1709
30 Does the mother work outdoors or indoors	0.03570	—	-0.16124	—	0.0330
31 Housekeeping help	0.03936	—	0.06729	—	-0.0720
32 Number of persons in the household	-0.03193	—	0.09396	—	0.1725
33 Number of children under 15 years of age	-0.32570	—	0.47893	—	-0.0184
34 Number of rooms	0.02388	0.08757	0.12387	-0.21732	-0.0221
35 Electricity in the house	-0.07143	—	-0.01352	—	0.018
36 Running water in the house	-0.01240	—	0.14740	—	0.082
37 Has the family house of its own	0.06568	—	0.00612	—	-0.063
38 Ownership of TV set	0.03591	—	0.11038	—	0.026
39 Ownership of car	0.12586	—	-0.07081	—	-0.225
40 Degree of industrialization of the place of residence	-0.07590	0.09324	0.12938	-0.20321	0.317
41 Character of the place of residence urban or rural	0.00452	—	-0.11829	—	-0.112
42 Internal migration	0.13728	0.06236	0.21094	-0.24046	0.143
43 Character f earlier place of residence	0.10813	0.07019	0.15516	-0.20329	-0.00
44 Distance to antenatal clinic	-0.07337	—	-0.03433	—	0.04
45 Distance to neighbour	-0.03440	—	-0.01747	—	-0.035
46 Distance to centres of population	-0.15701	0.04319	0.31743	-0.16138	0.24
47 Distanc to medical officer	0.29040	—	-0.26379	—	-0.14

calculated 1 on the total number of cases, 2. on the cases excluding intrauterine deaths, and 3 on the cases excluding all perinatal deaths Differences in the growth curves are only apparent before the 37th week of gestation the relative number of later deaths being small. The retardation of the curve in babies dying in utero alone seems to be of no practical importance, whereas the differing course of the curve plotted according to survivals alone is of practical significance before the 34th week of gestation

3 Perinatal mortality rate and birth weight correlated to maternal biological characteristics and socio-economic circumstances and prediction of the former from the latter

a. Discriminant function analyses

The eigenvectors, i.e discriminants, of analyses A A 1 B B 1 and C (see page 14) are presented in Table 10 The weighting of the variables is indicated as scaled and normalized o that the range of the weightings is from —1 to +1 and the sums of the squares of the weightings of each eigenvector is 1 The significance of the eigenvectors was tested with Rao s chi square approximation and the results are given below

Analysis	Number of variables	Eigen-vector	Chi square	Degrees of freedom	P
A	43	0 1896	56.3	43	< 0.001
A 1	27	0 1569	216 3	27	< 0.001
B	43	0 1508	160.3	43	< 0.001
B 1	27	0.1115	121.5	27	< 0 001
C	43	0 0655	69 6	43	< 0.01

The group means and group standard deviation in each analysis were as follows

Analysis	Controls Mean	Controls Standard deviation	Risk group Mean	Risk group Standard deviation
A	—1.871	0.530	—1.323	0.714
A 1	3.609	0.496	3 120	0.727
B	2.804	0.561	2.143	0.761
B 1	—3 422	0.547	—.864	0.750
C	10.681	0.785	10.026	0.825

The group means on the discriminants were relatively close to one another and group dispersions were to some extent overlapping

From the consideration of the group means the effect of the + or — sign of the weightings of the eigenvector can be seen The + sign indicates that high values of this variable are associated with the group with the higher mean and the — sign indicates that high values of this variable are associated with the group with the lower mean

In the different analyses the signs associated with membership of the different risk groups were A + A 1 — B — B 1 + C — In Table 10 the sign discriminating cases towards the risk group is given in front of each vector The higher the weighting of the variable the more important is the variable. Appendix 1 shows how each variable has been recorded For example, age is given in terms of the year of birth and since in the analyses an increasing score is associated with the control group low age is a characteristic of the control group while advancing age is associated with the risk group

The percentage distribution of the control and risk group cases on the basis of the classification procedure of discriminant function analyses A and C into different probability levels is presented in Fig 8 Probability in this context means that, if a case e.g has over 90 per cent probability of belonging to the low birth weight group, the discriminant score of the case is close to the point of maximum density of this group in discriminant space The empirical risk for such a case of giving birth to a low birth weight infant will be described further below (p 26)

TABLE 10 *Eigenvectors of discriminant function analyses A A1 B B1 and C Weightings of the variables have been scaled and normalized. A + sign on the top of a vector indicates that positive values of weightings of variables of this vector are associated with the risk group a − sign indicates that negative values of the weightings are associated with the risk group*

		A +	A1 −	B −	B1 +	C −
1	Maternal age	-0.30701	0.28671	0.18095	-0.24452	0.53295
2	Maternal height	-0.13111	0.12539	0.09841	-0.11054	0.29192
3	Maternal weight	-0.29079	0.34209	-0.01458	-0.04623	-0.08103
4	Menarche age	-0.06048	0.07505	0.00682	-0.03301	0.08721
5	Parity	-0.11849	0.41418	-0.14531	-0.33161	0.22475
6	Number of previous abortions	0.13198	-0.18172	-0.18746	0.28420	0.02541
7	Previous low birth weight infants	0.54215	-0.58377	-0.36805	0.30229	-0.02436
8	Previous perinatal mortality	0.00991	-0.06371	-0.04300	0.12671	0.02359
9	Mother marital status	0.28681	-0.33745	-0.19687	0.26361	0.03336
10	Mother occupation	0.12150	0.11143	-0.10814	-0.12531	0.01668
11	Father's occupation	0.07727	-0.13952	-0.03998	0.07613	-0.10335
12	Is the father a farmer	0.05262	0.06373	0.15182	-0.13532	-0.00031
13	Mother sector of economy	0.08473	—	-0.08506	—	-0.14689
14	Father sector of economy	-0.10100	—	0.11872	—	-0.11108
15	Mother's vocational standing	-0.04488	-0.12547	-0.10638	0.23207	0.02211
16	Father vocational standing	—	0.02523	—	-0.02541	—
17	Occupation of mother's father	0.03670	—	-0.10266	—	0.07279
18	Was mother's father farmer	-0.03561	—	0.05089	—	0.11866
19	Number of mother's siblings	-0.06419	—	-0.06302	—	0.22745
20	Number of mother's deceased siblings	0.03518	-0.03684	-0.09103	0.11038	-0.16221
21	Mother's school attendance	-0.01418	0.05838	0.06397	-0.12498	0.17217
22	Intellectual interest in house keeping and public health facilities	0.03453	-0.15381	-0.07437	0.22276	0.03307
23	Was the pregnancy wanted or not	—	-0.06685	—	-0.01100	—
24	Mother frame of mind during pregnancy	0.08396	-0.01370	-0.06293	0.05093	0.04839
25	Mother's attitude towards support by public authorities	—	0.02679	—	0.03491	—
26	Mother's smoking	0.20727	—	-0.12121	—	0.14322
27	Mother attitude to strenuousness of work	—	-0.02265	—	-0.03394	—
28	Mother gainful employment	-0.02363	-0.01734	0.02219	0.06952	0.13145
29	Posture at work	-0.04325	—	0.09389	—	0.17098
30	Does the mother work outdoors or indoors	0.03570	—	-0.16124	—	0.03308
31	Housekeeping help	0.03936	—	0.06729	—	-0.07207
32	Number of persons in the household	-0.03193	—	0.09396	—	0.17256
33	Number of children under 15 years of age	-0.32570	—	0.47893	—	-0.01848
34	Number of rooms	0.02388	0.08757	0.12387	-0.[illegible]1732	-0.02284
35	Electricity in the house	-0.07143	—	-0.01352	—	0.01847
36	Running water in the house	-0.01240	—	0.14740	—	0.08283
37	Has the family a house of its own	0.06568	—	0.00612	—	-0.06382
38	Ownership of TV set	0.03591	—	0.11038	—	0.02698
39	Ownership of car	0.12586	—	-0.07081	—	-0.22567
40	Degree of industrialization of the place of residence	-0.07590	0.09324	0.12938	-0.20321	0.31705
41	Character of the place of residence urban or rural	0.00452	—	-0.11829	—	-0.11230
42	Internal migration	0.13728	0.06234	0.21094	-0.24046	0.14332
43	Character of earlier place of residence	0.14813	0.07019	0.15516	-0.20529	-0.00049
44	Distance to antenatal clinic	-0.07337	—	-0.03433	—	0.04145
45	Distance to neighbour	-0.03440	—	-0.01747	—	-0.03502
46	Distance to centres of population	-0.15701	0.06319	0.31743	-0.16138	0.24615
47	Distance to medical officer	0.29040	—	-0.26379	—	-0.14649

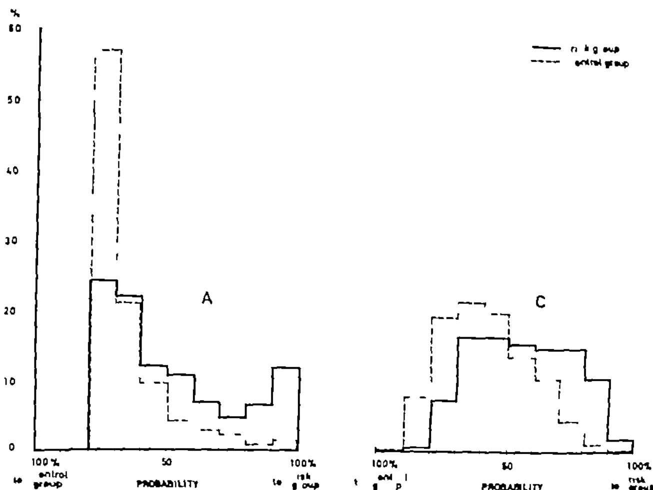


Fig 8 Percentage distribution of the control and risk group cases on the basis of the probability classification by discriminant function analyses A and C

A ... the analyses in which the two groups are controls and low birth weight infants
C ... the analyses in which the two groups are controls and perinatal deaths ... birth weight of 2500 g or more

As suggested by Rao s significance test the discriminating power of analysis C is less than that of analysis A This is also evident from Fig 8 The probability distributions of analysis A show distinct clusterings where the probability of right group membership is relatively high whereas in the probability distribution of analysis C the peak of the percentage clustering for both groups is close to the 50 per cent probability point

Table 11 shows the number of cases of analysed groups with over 50 per cent probability of risk group membership according to the different analyses. In a study like the present wh re the total distribution was very uneven or in other words the proportion of risk group in the total series was small

TABLE 11 *Probability distribution of cases in groups of discriminant function analyses towards risk groups in each analysis*

Analyses and their groups		Over 50 per cent probability of risk group membership	
		Number of cases	Per cent of total group
A	Control group	122	12.20
	Risk group	206	41.28
A 1	Control group	98	9.80
	Risk group	167	33.47
B	Control group	110	11.00
	Risk group	69	42.07
B 1	Control group	115	11.50
	Risk group	59	35.98
C	Control group	303	30.30
	Risk group	69	57.98

It is essential for the identification of risk group cases that the percentage of cases falsely included in the risk group is low compared with the total number of cases. This may be considered to be the case at 50 per cent probability level in analyses A, A 1 B and B 1 that is to say in all analyses concerned with the low birth weight babies, since the percentage of falsely classified control group cases was 9.8—12.2 per cent. By contrast, in analysis C which concerns infants with a minimum birth weight of 2500 g, 30.3 per cent of the controls were included in the risk group at the 50 per cent probability level.

b *Result of probability classification of total series on the basis of the discriminant function analysis concerned with low birth weight infants*

The cases not involved in the analysis itself were also classified by the analysis A classification programme. These three groups are listed below together with the percentage of cases with over 50 per cent probability of risk group membership.

Classified group	Total cases in the group	Over 50 per cent probability of risk group membership	
		Number of cases	Per cent of total group
Birth weight ≥ 2500 g, deaths	119	22	18.49
Birth weight ≥ 2500 g, gestational age ≤ 37 weeks, survivals	696	133	19.11
Birth weight ≥ 2500 g, gestational age ≥ 43 weeks, survivals	617	71	11.53

Table 12 shows the probability based on classification of all cases by analysis A, of risk group membership at 10 per cent intervals. Table 13 gives, separately the probability classification of all perinatal deaths, with mortality rates, while Table 14 presents the relevant low birth weight rates. A study of the results concerned with mortality rates and low birth weight rates yields four groups probability ranges 20—30 per cent, 30—50 per cent, 50—80 per cent, and over 80 per cent, the percentages indicating the degree of probability of risk group membership. The probabilities obtained for all cases combined by this method are shown in Table 15 both for the total number of cases, mortality rates and low birth weight rates. The empirical risk of mothers in the probability ranges determined by the discrimination scores giving birth to a child of low birth weight can now be established: in the range 20—30 per cent it is 1.9 per cent, 30—50 per cent 4.6 per cent, 50—80 per cent 9.2 per cent, and 80—100 per cent 22.0 per cent (Table 15).

The cases were thus divided into the following four groups.

Low risk groups

1. 20—30 per cent probability of membership of the low birth weight group. This group comprised just over half the total number of cases. The low birth weight rate was less than half the rate of the initial series. The mortality rate was 30 per cent lower than that of the initial series.
2. 30—50 per cent probability of membership of the low birth weight group. One-third of the total number of cases belonged to this group. Both the low birth weight rate and mortality rate were slightly higher than, yet of the same order of magnitude as, in the initial series.

High risk groups

3. 50—80 per cent probability of membership of the low birth weight group. This group comprised one-tenth of the total number of cases. The low birth weight rate was

TABLE 12 *Distribution of all cases on the basis of the probability classification by analysis A The result is indicated as the probability of risk group membership*

Birth weight groups	Probabilities of membership of group with birth weight under 2500 g, per cent									
	0—20	20—30	30—40	40—50	50—60	60—70	70—80	80—90	90—100	Total
under 2500 g, all	0	122	110	61	53	35	24	34	60	499
2500 g or more, perinatal deaths	0	55	30	12	10	6	3	1	2	115
2500 g or more gestation 38—42 weeks, survivals	0	5,700	2,100	980	440	290	230	100	160	10,000
2500 g or more, gestation 37 weeks or less, survivals	0	350	153	60	44	27	13	24	25	696
2500 g or more, gestation 43 weeks or more survivals	0	333	156	57	22	14	13	15	7	617
Total	0	6,560	2,549	1 170	569	372	283	174	254	11 931

TABLE 13 *Distribution of perinatal deaths by probability classification of analysis A and mortality rates per thousand by degrees of probability The result is indicated as the probability of risk group membership*

	Probabilities of membership of group with birth weight under 2500 g, per cent								
	20—30	30—40	40—50	50—60	60—70	70—80	80—90	90—100	Total
Deaths	106	61	31	30	14	10	11	[illegible]	[illegible]
Total number of the group	6,560	2,549	1 170	569	372	283	174	254	11 931
Mortality rate per thousand	16.2	23 9	26.5	52.7	37 6	35.3	63.2	78.7	23.7

TABLE 14 *Distribution of low birth weight infants by probability classification of ana- lysis A and percentages of the low birth weight infants by degrees of probability The result is indicated as the probability of risk group membership*

	Probabilities of membership of group with birth weight under 2500 g, per cent								
	20—30	30—40	40—50	50—60	60—70	70—80	80—90	90—100	Total
Number of low birth weight infants	122	110	61	53	35	24	34	60	499
Total number of the group	6,560	2,549	1 170	569	372	283	174	254	11 931
Low birth weight rate per cent	1 9	4.3	5.2	9.3	9 4	8.5	19.5	23.6	4.2

TABLE 15 *Distribution of the total number of cases using four probability ranges by probability classification of analysis A mortality rates and low birth weight rates*

	Probabilities of membership of group with birth weight under 2500 g, per cent.				
	20—30	30—50	50—80	80—100	Total
Total number of the group	6,560	3,719	1,224	428	11 931
Low birth weight rate per cent	1 9	4.6	9.2	[illegible]	4.2
Mortality rate, per thousand	16.2	24.7	44 1	72.4	23.7

TABLE 16. *Means and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1—4 formed on the basis of the probability levels obtained from discriminant function analysis A.*

	Low risk groups 1	2	High risk groups 3	4	Total cases
Mean birth weight, g	3544±326	3408±333	3183±396	2974±744	3444±369
Mean length at birth, cm	50.6±2.3	50.1±2.3	49.3±2.9	48.1±3.8	50.2±2.5

more than twice, and the mortality rate nearly twice that of the initial series.

4 over 80 per cent probability of *membership* of the low birth weight group. The group comprised some 3.5 per cent of the total number of cases. The low birth weight rate was five times and the mortality rate more than three times that of the initial series.

Thus classification into *low risk and high risk groups* will be used in the following. Table 16 presents the mean values and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1—4. The differences from one group to the other are evident, the birth weight and length at birth diminishing as the probability of risk increases.

False classification may be assumed in all those cases from the high risk groups in which the child survived and had a minimum birth weight of 2500 g. For this reason, the mean birth weights of these children were calculated separately and in groups 1-4 were *3577, 3495* 3321 and 3292 g, respectively. Since the low risk group 1 comprises more than half the total number of cases, the infants with the lowest probability of risk group membership, under the 22.5 per cent probability level, were examined separately. These cases numbered 1011; their mean birth weight was 3771 ± 472 g and mean length at birth 51.4 ± 1.8 cm. *Since the birth weights of the falsely* classified were markedly lower than those of the correctly classified, one may ask whether the classification really was *false* and take it that the infants of a minimum birth weight of 2500 g and living beyond the perinatal period very largely represented the biological variation inside the high risk group.

Survival might also be measured as a continuous variable which would indicate the different degrees of health. It could not be used for the present purpose, and in analysis A, the group consisting of all low birth weight infants, the increased mortality rate of the high risk group may be considered as associated with their low birth weight. The following calculation was made to prove this. The mortality in the total number of cases per each 500 gram weight range was calculated (Tables *27* and *28* in Appendices 2 and 3), and according to this mean the number of deaths which risk groups 3 and 4 ought to show on the basis of their combined weight distribution was estimated. The number of deaths predicted in this way was 93, while the true number was 85. The difference in the numbers is not statistically significant, and therefore the increased mortality of the risk group of analysis A can be assumed to be associated with low birth weight.

For a more detailed study of the characteristics of risk group infants, the low and high risk groups 1—2 and 3—4 were combined since the number of cases in the latter groups was small. They displayed the following characteristics

TABLE 12 *Distribution of all cases on the basis of the probability classification by analysis A The result is indicated as the probability of risk group membership*

Birth weight groups	Probabilities of membership of group with birth weight under 2500 g, per cent.									
	0—20	20—30	30—40	40—50	50—60	60—70	70—80	80—90	90—100	Total
under 2500 g, all	0	122	110	61	53	35	24	34	60	499
2500 g or more perinatal deaths	0	55	30	12	10	6	3	1	2	119
2500 g or more gestation 38—42 weeks, survivals	0	5,700	2,100	980	440	290	230	100	160	10,000
2500 g or more, gestation 37 weeks or less, survivals	0	350	153	60	44	27	13	24	25	696
2500 g or more gestation 43 weeks or more survivals	0	333	156	57	2[illegible]	14	13	15	7	617
Total	0	6,560	2,549	1 170	569	372	283	174	254	11,931

TABLE 13 *Distribution of perinatal deaths by probability classification of analysis A and mortality rates per thousand by degrees of probability The result is indicated as the probability of risk group membership*

	Probabilities of membership of group with birth weight under 2500 g, per cent.								
	20—30	30—40	40—50	50—60	60—70	70—80	80—90	90—100	Total
Deaths	106	61	31	30	14	10	11	20	283
Total number of the group	6,560	2,549	1 170	569	372	283	174	254	11 931
Mortality rate per thousand	16.[illegible]	23.9	26.5	52.7	37.6	35.3	63.[illegible]	78.7	23.7

TABLE 14 *Distribution of low birth weight infants by probability classification of analysis A and percentages of the low birth weight infants by degrees of probability The result is indicated as the probability of risk group membership*

	Probabilities of membership of group with birth weight under 2500 g, per cent.								
	20—30	30—40	40—50	50—60	60—70	70—80	80—90	90—100	Total
Number of low birth weight infants	122	110	61	53	35	4	34	60	499
Total number of the group	6,560	2,549	1 170	569	372	283	174	254	11 931
Low birth weight rate per cent	1.9	4.3	5.2	9.3	9.4	8.5	19.5	23.6	4.2

TABLE 15 *Distribution of the total number of cases using four probability ranges by probability classification of analysis A mortality rates and low birth weight rates*

	Probabilities of membership of group with birth weight under 2500 g, per cent.				
	20—30	30—50	50—80	80—100	Total
Total number of the group	6,560	3,719	1,224	428	11 931
Low birth weight rate, per cent	1.9	4.6	9.2	22.0	4.2
Mortality rate per thousand	16.2	24.7	44.1	72.4	23.7

TABLE 16. *Means and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1—4 formed on the basis of the probability levels obtained from discriminant function analysis A*

	Low risk groups		High risk groups		Total cases
	1	2	3	4	
Mean birth weight, g	3544±526	3408±533	3183±596	2974±744	3444±569
Mean length at birth, cm	50.6±2.3	50.1±2.5	49.3±2.9	48.1±3.8	50.2±2.5

more than twice, and the mortality rate nearly twice that of the initial series.

4 over 80 per cent probability of membership of the low birth weight group. The group comprised some 3.5 per cent of the total number of cases. The low birth weight rate was five times and the mortality rate more than three times that of the initial series.

This classification into *low risk and high risk groups* will be used in the following.

Table 16 presents the *mean values* and standard deviations of birth weights and lengths at birth in the low risk and high risk groups 1—4. The differences from one group to the other are evident, the birth weight and length at birth diminishing as the probability of risk increases.

False classification may be assumed in all those cases from the high risk groups in which the child survi ed and had a minimum birth weight of 2500 g. For this reason, the mean birth weights of these children were calculated separately and in groups 1–4 were 3577 3495 3321 and 3292 g, respectively Since the low risk group 1 *comprises more than half* the total number of cases, the infants with the lowest probability of risk group membership, under the 22.5 per cent *probability level, were* examined separately These cases numbered 1011 their mean birth weight was 3771 ± 472 g and mean length at birth 51.4 ± 1.9 cm. Since the birth weights of the *falsely classified were markedly lower than those of* the incorrectly classified, one may ask whether the classification really was false and take it that the infants of a *minimum* birth weight of 2500 g and living beyond the perinatal period very largely represented the biological *variation inside the high risk group*

Survival might also be measured as a continuous variable which would indicate the *different degrees of health. It could not be* used for the present purpose, and in analysis A, the group consisting of all low birth weight infants, the *increased mortality rate* of the high risk group *may be considered* as associated with their low birth weight. The following calculation was *made to prove this*. The mortality in the total number of cases per each 500 gram weight range was calculated (Tables *27* and *28* in Appendices 2 and 3), and according to this mean the number of deaths which risk groups 3 and 4 ought to show on the basis of their combined weight distribution was estimated. The number of deaths predicted in this way was 93 while the true number was 85. The difference in the numbers *is not statistically significant,* and therefore *the increased mortality of the risk group of analysis A can be assumed to be* associated with *low birth weight.*

For a more detailed study of the characteristics of risk group infants, the low and high risk groups 1—2 and 3—4 were combined since the number of cases in the latter groups was small. They displayed the following characteristics.

	Low risk group	High risk group
Number of cases	10,279	1,652
Boys/1000 girls	1 111	910
Mean birth weight, g	3495±540	3129±644
Mean length at birth, cm	50.4±.-.3	49.0±3.2
Mean gestational age, days	278±14.0	272.7±19.2
Low birth weight rate, per cent	2.8	12.5
Perinatal mortality rate, per 1000	19.3	51 4

If the high risk group is studied by 100 gram weight groups, the majority of cases was in group 3100-3199 g 10 2 per cent while the weight range of 3100-3399 g covered 26 2 per cent. In the low risk group the majority of cases, 9 0 per cent was in the 3500—3599 g group while weight range 3500—3799 g covered 26 3 per cent

Table 17 shows the percentage composition of the 500 gram weight classes in high and low risk groups, and Table 18 presents the distribution of gestational weeks in these groups. The result was more conclusive for birth weight over 50 per cent of the lowest weight group was composed of the high risk group and the share decreased regularly on transition to the higher weight groups so that birth weights exceeding 4500 g equalled only about 3 per cent of the high risk group The study of gestational age gave a parallel result

TABLE 17 *Distribution of cases from the different weight groups into high risk and low risk groups on the basis of the probability classification by discriminant function analysis A*

Weight groups g	High risk group		Low risk group		Total	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
less than 1500	49	51.6	46	48.4	95	100 0
1500—1999	40	40.0	60	60.0	100	100.0
2000—2499	117	38.5	187	61 5	304	100.0
2500—2999	292	22.3	1,018	77.7	1,310	100.0
3000—3499	642	16.6	3.225	83 4	3,867	100.0
3500—3999	401	9 1	4,013	90 9	4 414	100.0
4000—4499	99	6.8	1,351	93.2	1 450	100.0
4500—4999	10	3 1	314	96.9	324	100.0
5000 and more	2	3.0	65	97.0	67	100.0
Total	1,652	13.8	10,279	86..	11 931	100.0

TABLE 18 *Distribution of cases from the different gestational age groups into high risk and low risk groups on the basis of the probability classification by discriminant function analysis A*

Week of gestation	High risk group		Low risk group		Total	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
25— 6	6	35 3	11	64.7	17	100.0
27—29	16	42 1	22	57 9	38	100.0
30—32	31	38.7	49	61.3	80	100.0
33—35	77	26 5	214	73.5	291	100.0
36—38	237	17 1	1 149	82.9	1,386	100.0
39—41	997	13 4	6 434	86.6	431	100.0
42—44	233	10 4	1 997	89.6	230	100 0
45 or more	9	14.3	54	85 7	63	100.0
Total	1,606	13 9	9 930	86.1	11,336	100 0

TABLE 19 *Location of the high risk and low risk group cases by the probability classification of discriminant function analysis A of all low birth weight infants in the zones determined by the percentiles of the intrauterine growth curve of the total number of cases*

	Location of the cases on the intrauterine growth curve							
	Below 10th percentile		Between 10th and 50th percentiles		Between 50th and 90th percentiles		Above 90th percentile	
	Number of cases	Per cent of total zone	Number of cases	Per cent of total zone	Number of cases	Per cent of total zone	Number of cases	Per cent of total zone
High risk group	270	26.9	842	16.4	462	10.4	32	3.3
Low risk group	732	73.1	4,278	83.6	3,971	89.6	949	96.7
Total	1,002	100.0	5,120	100.0	4 433	100.0	981	100.0

TABLE 20 *Mean birth weights of the high risk and low risk group cases at given gestational ages on the basis of the probability classification by discriminant function analysis A of all low birth weight infants and t for the significance of the difference in mean birth weights (*P< 0.10 P<0.05 P<0.01)*

Week of gestation	High risk group		Low risk group		t for difference in mean birth weights
	Number of cases	Mean birth weight, g	Number of cases	Mean birth weight, g	
25—26	6	1,017	11	1,082	0.58
27—28	11	1,282	14	1,093	2.12
29—30	16	1 450	23	1,596	1.89*
31—32	20	1,835	34	2,068	2.96
33—34	44	2,309	98	2,691	7.83
35—36	85	2,656	293	2,938	9.47*
37—38	185	2,936	972	3,231	15.56
39—40	725	3,255	3 972	3 470	25.31
41—42	438	3,396	3 944	3,676	25.72
43—44	67	3,330	506	3,709	12.82
Over 44 or not known	55	2,676	403	3,318	19.31
Total	1,652	3 129	10,279	3,495	58.64

though the decrease was less abrupt. Before the 33rd week of gestation, the high risk group comprised 35—42 per cent and from the 39th week onwards 10—14 per cent of the gestational age groups.

Table 19 specifies the high and low risk groups in the percentile zones of the intrauterine growth curve. If the location of high risk cases is reviewed by number it is found that nearly 9 times as many cases are located below the 10th percentile as above the 90th percentile, while nearly twice as many cases are located between the 10th and 50th as between the 50th and 90th percentiles. 26.9 per cent of all cases located below the 10th and 3.3 per cent of those located above the 90th percentile belonged to the high risk group.

Table 20 gives the mean birth weights of the high and low risk cases when the groups

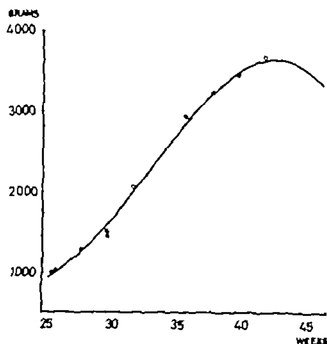


Fig 9 The 50th percentile intrauterine growth curve of the total number of cases and the mean birth weights by week of gestation in the groups obtained from probability classification by discriminant function analysis A which concerned all low birth weight infants.
● high risk group
O low risk group

are divided into fortnightly periods by gestational age From the 29th to 30th gestational week onwards the birth weights of the high risk group were lower and the difference was statistically highly significant from the 31st to 32nd week onwards. The findings are plotted in the graph of Fig 9

The high risk group contained relatively fewer boys per 1000 girls than the initial series, in the former 910 and in the latter 1086 The difference was statistically highly significant.

c Variables used in discriminant function analysis

The greater the weighting of a variable on the eigenvector the greater part that variable plays in the discriminant function There is, however no specific test to indicate the significance of the weighting

The 15 variables with the highest weighting in discriminant function *analysis A* are listed below biological characteristics and socio-economic circumstances separately but otherwise in order of decreasing power of discrimination. The characteristic of the variables tending to increase the risk is indicated and the ordinal number of the variable in Table 10 is given in brackets.

— Previous low birth weight infants (7)
— Small number of children under 15 years of age (33)
— Advancing age (1)
— Low maternal weight (3)
— *Previous abortions (6)*
— Small maternal stature (2)
— Low parity (5)

— Long distance to medical officer (47)
— Illegitimacy (9)
— Smoking (26)
— Short distance to centres of population (46)
— Internal migration (42)
— The family has no car (39)
— Mother's occupation belongs to a low social group (10)
— Earlier domicile in remote district (43)

Distributions and mean values of the most important biological variables in the low risk and high risk groups 1—4 are given in Table 21 those of the main socio-economic variables in Table 22 The means were calculated on the cases in which the value of the relevant variable was known the missing observations were not corrected but these cases were excluded This provides a descriptive picture of the function of the variables yet it should be borne in mind that discriminant function analysis is a linear combination of all the variables involved, many variables having a reverse effect on the mean value characteristics of the group For example, the most potent discriminant in analysis A previous low birth weight infants, excludes all primiparas. On the other hand with increasing number of primiparas the mean age of the group is reduced and the influence of advancing age becomes visible after a given parity level The effect

TABLE 21 *Distributions and mean values of biological characteristics among mothers of the low risk and high risk groups formed on the basis of probability classification by discriminant function analysis A of all low birth weight infants*

Variables	Low risk groups		High risk groups		Total number of cases
	1	2	3	4	
Percentage with previous low birth weight infants	2.9	5 6	26.7	38.6	8.4
Percentage with previous abortions	14.0	18.6	25.6	25.1	17.0
Primipara, per cent	24.2	43.9	44 1	32.9	32.7
Mean age of primiparas, years	22.2	22.9	24 1	23 1	22.8
Mean number of children under 15 of para II	0.96	0.94	0.94	0.78	0.95
Mean number of children under 15 of para IV	2.76	2.47	2.51	1.69	2.64
Mothers' mean weight, kg	61.9	56.7	55.2	55.5	59.3
Mothers' mean height, cm	161.2	159 4	157.5	157 4	160.1

TABLE 22. *Distributions and mean values of socio-economic circumstances of mothers of the low risk and high risk groups formed on the basis of probability classification by discriminant function analysis A of all low birth weight infants*

Variables	Low risk groups		High risk groups		Total number of cases
	1	2	3	4	
Illegitimate, per cent	0.2	3.7	13.2	40.7	5.0
Smokers, per cent	10.2	32 4	40 0	48.0	21.5
Social group I according to the mother own occupation, per cent	4 2	2.3	1.8	0.7	3.3
Social group IV according to the mother' own occupation, per cent	4.7	6 1	12.1	27.2	6.6
Car owners, per cent	50.1	27.8	21 9	23 1	39 4
Moved to another place of residence, per cent	65 9	67.8	68.4	68.8	66.9
Mo ed from urban place of residence, per cent of all migrants	9 3	7.5	6.3	11.8	8.5
Moved from remote village, per cent of all migrants	53 9	61 1	73.5	54.2	58.2
Distance to medical officer mean alue, km	15.7	15.8	22.8	23.5	16.7

of a ariable may sometimes be seen only f certain other variables remain constant.

A variable of high weighting and consequently high discriminant function, here included in the biological variables, is the number of children under 15 years of age. In the original questionnaire this variable was included among the questions measuring the amount of work the mother does. It is, how ever obvious that the function of this variable is not concerned with working capacity but is a biological characteristic. It contains combined information on parity interval between pregnancies, and deaths of previous

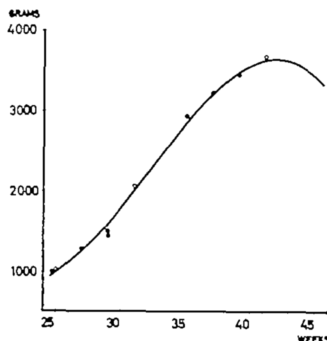


Fig 9 The 50th percentile intrauterine growth curve of the total number of cases and the mean birth weights by week of gestation in the groups obtained from probability classification by discriminant function analysis A which concerned all low birth weight infants.
● *high risk group*
O *low risk group*

are divided into fortnightly periods by gestational age From the 29th to 30th gestational week onwards the birth weights of the high risk group were lower and the difference was statistically highly significant from the 31st to 32nd week onwards. The findings are plotted in the graph of Fig 9

The high risk group contained relatively fewer boys per 1000 girls than the initial series, in the former 910 and in the latter 1086 The difference was statistically highly significant.

c Variables used in discriminant function analysis

The greater the weighting of a variable on the eigenvector the greater part that variable plays in the discriminant function There is, however no specific test to indicate the significance of the weighting

The 15 variables with the highest weighting in discriminant function *analysis A* are listed below biological characteristics and socio-economic circumstances separately but otherwise in order of decreasing power of discrimination. The characteristic of the variables tending to increase the risk is indicated and the ordinal number of the variable in Table 10 is given in brackets

— Previous low birth weight infants (7)
— Small number of children under 15 years of age (33)
— Advancing age (1)
— Low maternal weight (3)
— Previous abortions (6)
— Small maternal stature (2)
— Low parity (5)

— Long distance to medical officer (47)
— Illegitimacy (9)
— Smoking (26)
— Short distance to centres of population (46)
— Internal migration (42)
— The family has no car (39)
— Mother's occupation belongs to a low social group (10)
— Earlier domicile in remote district (43)

Distributions and mean values of the most important biological variables in the low risk and high risk groups 1—4 are given in Table 21 those of the main socio-economic variables in Table 22 The means were calculated on the cases in which the value of the relevant variable was known the missing observations were not corrected but these cases were excluded This provides a descriptive picture of the function of the variables, yet it should be borne in mind that discriminant function analysis is a linear combination of all the variables involved, many variables having a reverse effect on the mean value characteristics of the group For example, the most potent discriminant in analysis A, previous low birth weight infants, excludes all primiparas. On the other hand, with increasing number of primiparas the mean age of the group is reduced and the influence of advancing age becomes visible after a given parity level The effect

lysis C, the 15 variables with the highest weightings, divided into biological characteristics and socio-economic circumstances but otherwise in descending order of discriminant power are as follows

- Advancing age (1)
- Small maternal stature (2)
- Low parity (5)
- Small number of members in the household (32)
- Low degree of industrialization of the place of residence (40)
- Short distance to centres of population (46)
- Small number of mother's siblings (19)
- No car in the family (39)
- Low level of school attendance (21)
- Sitting work posture of the mother (?9)
- Many of the mother's siblings have died (20)
- Mother is employed in service industry (13)
- Long distance to medical officer (47)
- No internal migration (42)
- Non-smoker (26)

The variables essential for the discriminant function of analysis C but absent among the important variables of analyses A and B are small umber of mother's siblings, large number of dead siblings, small size of household, low level of school attendance, sedentary work, and employment in a service industry

Table 23 presents some mean values and distributions of variables typical of the risk groups of analysis C. Not all cases were classified by analysis C, and for this reason the risk group is represented by only 50 mothers who had given birth to a child with a birth weight of 2500 g or more which had died in the perinatal period, and to whom the analysis had accorded a probability of over 60 per cent of risk group membership. Had the chosen probability level been 50 per cent, 30 per cent of the control cases would have belonged to the risk group for which reason the over-60 per cent probability level was adopted, with which only 16.4 per cent of the controls entered the risk group. The control group in Table 23 consisted of the distribution of variables equalling that in the total number of cases.

If on the basis of the above the important variables of analysis C are reviewed against those of analyses A and B, analysis C is seen to be no more similar to A than B This conclusion was re-examined by classifying the 119 cases of perinatal deaths with birth weights of 2500 g or more, which made up the risk group of analysis C, using the probability classification of both A and B analyses. With a probability level of 50 per cent or over on analysis A, 22 were placed in the risk group and on analysis B, 21 were placed in the risk group Hence these two analyses may be considered to place equal numbers from the risk group of analysis C into their respective risk groups. Comparing the effect of analyses A and B on the low birth weight perinatal

TABLE 23 *Discriminant function analysis C of perinatal deaths of infants with birth weights of 2500 g o more Distributions and mean values of characteristics of 50 mothers with 60—100 probability of risk group membership The corresponding values for all the cases are given*

Variables	Included in risk group with 60—100 per cent probability	Total number of cases
Mother's siblings, mean number	4 9	5.4
Mother's siblings, mean number of deaths	1 14	0.83
School attendance beyond primary school, per cent of mothers	8.1	18 4
Work mainly sedentary per cent of mothers	46.1	12.4
Mean development score of the place of residence	3.7	5.2

children The question concerned the number of children in a particular mother s household and the reply for mothers living in extended family households also contains information about children other than those of the particular mother herself In the present study more than 10 per cent of primiparas, who cannot have had children of their own lived in households with children under 15 years of age In the combined high risk group the percentage was 12 and combined low risk group 15 per cent of primiparas, whereas in the higher parity classes the figure apparently is much lower Since Table 21 for the mean number of children under 15 in the households of parity 2 and 4 mothers, makes an effort to include the mothers own children only the means have been calculated excluding for parity 2 all figures in excess of one and for parity 4 all figures in excess of 3 This method, naturally has also excluded the mothers with earlier multiple births, but this is of no importance in comparing the means of the different groups.

In discriminant function *analysis B* that is to say the one concerned with the dead low birth weight infants, the following 15 variables had the highest weighting The variables are again divided into biological characteristics and socio-economic circumstances but otherwise they are in the order of importance.

— Small number of children under 15 years of age (33)
— Previous low birth weight infants (7)
— Previous abortions (6)
— Advancing age (1)
— High parity (5)

— Short distance to centre of population (46)
— Long distance to medical officer (47)
— No change of residence (42)
— Illegitimacy (9)
— Place of work as much indoors as outdoors (30)
— Earlier place of residence close to population centre (43)
— Child s father is not farmer (12)
— Running water at home (36)
— Low degree of industrialization in place of residence (40)
— Few rooms at home (34)

The importance of the variables of two discriminant function analyses can be compared by studying the weighting the variables acquire on the eigenvector provided the two analyses have the same power of discrimination and all the variables used are the same. This is true of analyses A and B In analysis A the weighting of the most important variables is higher than that of analysis B the 15th highest weighting in analysis A was 0 108 in analysis B 0 124 On this basis it may be said that in analysis B the sum of squares which is 1 available for the normalization of the weightings, is divided more uniformly on several variables than in analysis A. For this reason the discrimination significance attributable to the best 15 discriminants in analysis A may be considered in analysis B to divide itself between the 15 variables of the highest 15 weightings and the next 5 which were

— Smoking (26)
— Present place of residence in remote district (41)
— Father makes a living in agriculture (14)
— *No television in the family* (38)
— Social group according to mother s occupation is low (10)

The significant variables of analysis B which were not essential in analysis A may according to their content be grouped as follows family makes its living in agriculture but father is not a farmer the family is destitute and lives in underdeveloped district (variables 12, 14 30 34 38 40 and 41 in Table 10 page 23)

Analysis C the discriminant function analysis concerned with perinatal deaths with birth weight of 2500 g or more, has a poorer discriminant power than analyses A and B and for this reason the weightings of the variables are not directly comparable In ana

lysis C, the 15 variables with the highest weightings, divided into biological characteristics and socio-economic circumstances but otherwise in descending order of discriminant power are as follows:

— Advancing age (1)
— Small maternal stature (2)
— Low parity (5)
— Small number of members in the household (32)
— Low degree of industrialization of the place of residence (40)
— Short distance to centres of population (46)
— Small number of mother's siblings (19)
— No car in the family (39)
— Low level of school attendance (21)
— Sitting work posture of the mother (29)
— Many of the mother's siblings have died (20)
— Mother is employed in service industry (13)
— Long distance to medical officer (47)
— No internal migration (42)
— Non-smoker (26)

The variables essential for the discriminant function of analysis C but absent among the important variables of analyses A and B are small number of mother's siblings, large number of dead siblings, small size of household, low level of school attendance, sedentary work, and employment in a service industry

Table 23 presents some mean values and distributions of variables typical of the risk *groups of analysis* C. Not all cases were classified by analysis C, and for this reason the risk group is represented by *only* 50 mothers who had given birth to a child with a birth weight of 2500 g or more which had died in the perinatal period, and to whom the analysis had accorded a probability of over 60 per cent of risk group membership Had the chosen probability level been 50 per cent, 30 per cent of the control cases would have belonged to the risk group, for which reason the over-60 per cent *probability level* was adopted, with which only 16.4 per cent of the controls entered the risk group The control group in *Table 23 consisted of the* distribution of variables equalling that in the total number of cases.

If on the basis of the above, the important variables of analysis C are reviewed against those of analyses A and B analysis C is seen to be no more similar to A than B. This conclusion was re-examined by classifying the 119 cases of perinatal deaths with birth weights of 2500 g or more, which made up the risk group of analysis C, using the probability classification of both A and B analyses. With a probability level of 50 per cent or over on analysis A, 22 were placed in the risk *group and on analysis B, 21 were placed in* the risk group. Hence these two analyses may be considered to place equal numbers from the risk group of analysis C into their respective risk groups. Comparing the effect of analyses A and B on the low birth weight perinatal

TABLE 23 *Discriminant function analysis C of perinatal deaths of infants with birth weights of 2500 g or more Distributions and mean values of characteristics of 50 mothers with 60—100 probability of risk group membership The corresponding values for all the cases are given.*

Variables	Included in risk group with 60—100 per cent probability	Total number of cases
Mother siblings, mean number	4.9	5 4
Mother siblings, mean number of deaths	1 14	0.83
School attendance beyond primary school, per cent of mothers	8.1	18.4
Work mainly sedentary per cent of mothers	26.1	12.4
Mean development score of the place of residence	3.7	3.2

children The question concerned the number of children in a particular mother's household, and the reply for mothers living in extended family households also contains information about children other than those of the particular mother herself In the present study more than 10 per cent of primiparas, who cannot have had children of their own lived in households with children under 15 years of age In the combined high risk group the percentage was 12 and combined low risk group 15 per cent of primiparas whereas in the higher parity classes the figure apparently is much lower Since Table 21 for the mean number of children under 15 in the households of parity 2 and 4 mothers, makes an effort to include the mothers own children only the means have been calculated excluding for parity 2 all figures in excess of one and for parity 4 all figures in excess of 3 This method, naturally has also excluded the mothers with earlier multiple births, but this is of no importance in comparing the means of the different groups

In discriminant function *analysis B* that is to say the one concerned with the dead low birth weight infants, the following 15 variables had the highest weighting The variables are again divided into biological characteristics and socio-economic circumstances but otherwise they are in the order of importance.

— Small number of children under 15 years of age (33)
— Previous low birth weight infants (7)
— Previous abortions (6)
— Advancing age (1)
— High parity (5)

— Short distance to centre of population (46)
— Long distance to medical officer (47)
— No change of residence (42)
— Illegitimacy (9)
— Place of work as much indoors as outdoors (30)
— Earlier place of residence close to population centre (43)
— Child s father is not farmer (12)
— Running water at home (36)
— Low degree of industrialization in place of residence (40)
— Few rooms at home (34)

The importance of the variables of two discriminant function analyses can be compared by studying the weighting the variables acquire on the eigenvector provided the two analyses have the same power of discrimination and all the variables used are the same. This is true of analyses A and B In analysis A the weighting of the most important variables is higher than that of analysis B the 15th highest weighting in analysis A was 0 108 in analysis B 0 124 On this basis it may be said that in analysis B the sum of squares which is 1 available for the normalization of the weightings, is divided more uniformly on several variables than in analysis A. For this reason, the discrimination significance attributable to the best 15 discriminants in analysis A may be considered, in analysis B to divide itself between the 15 variables of the highest 15 weightings and the next 5 which were

— Smoking (26)
— Present place of residence in remote district (41)
— Father makes a living in agriculture (14)
— No television in the family (38)
— Social group according to mother s occupation is low (10)

The significant variables of analysis B which were not essential in analysis A may according to their content, be grouped as follows family makes its living in agriculture but father is not a farmer the family is destitute and lives in underdeveloped district (variables 12 14 30 34 38 40 and 41 in Table 10 page 23)

Analysis C the discriminant function analysis concerned with perinatal deaths with birth weight of 2500 g or more has a poorer discriminant power than analyses A and B and for this reason the weightings of the variables are not directly comparable In ana

lysis C, the 15 variables with the highest weightings, divided into *biological characteristics* and socio-economic circumstances but otherwise in descending order of discriminant power are as follows.

— Advancing age (1)
— Small maternal stature (2)
— Low parity (5)
— Small number of members in the household (32)
— Low degree of industrialization of the place of residence (40)
— Short distance to centres of population (46)
— Small number of mother's siblings (19)
— No car in the family (39)
— Low level of school attendance (21)
— Sitting work posture of the mother (29)
— Many of the mother's siblings have died (20)
— Mother is employed in service industry (13)
— Long distance to medical officer (47)
— No internal migration (42)
— Non-smoker (26)

The variables essential for the discriminant function of analysis C but absent among the important variables *of analyses A and B are* small number of mother's siblings, large number of dead siblings, small size of household, low level of school attendance sedentary work, and employment in a service industry.

Table 23 presents some mean values and distributions of variables typical of the risk groups of analysis C. Not all cases were classified by analysis C, and for this reason the risk group is *represented by only 50* mothers who had given birth to a child with a birth weight of 2500 g or more which had died in the perinatal period, and to whom the analysis had accorded a probability of over 60 per cent of risk group membership. Had the chosen probability level been 50 per cent, 30 per cent of the control cases would have belonged to the risk group, for which reason the over-60 per cent probability level was adopted, with which only 16.4 per cent of the controls entered the risk group. The control group in Table 23 consisted of the distribution of variables equalling that in the total number of cases.

If on the basis of the above, the important variables of analysis C are reviewed against those of analyses A and B, analysis C is seen to be no more similar to A than B. This conclusion was re-examined by classifying the 119 cases of perinatal deaths with birth weights of 2500 g or more, which made up the risk group of analysis C, using the probability classification of both A and B analyses. With a probability level of 50 per cent or over on analysis A, 22 were placed in the risk group and on analysis B 21 were placed in the risk group. Hence these two analyses may be considered to place equal numbers from the risk group of analysis C into their respective risk groups. Comparing the effect of analyses A and B on the low birth weight perinatal

TABLE 23 *Discriminant function analysis C of perinatal deaths of infants with birth weights of 2500 g or more. Distributions and mean values of characteristics of 50 mothers with 60—100 probability of risk group membership. The corresponding values for all the cases are given.*

Variables	Included in risk group with 60—100 per cent probability	Total number of cases
Mother siblings, mean number	4.9	5.4
Mother siblings, mean number of deaths	1.14	0.83
School attendance beyond primary school, per cent of mothers	8.1	18.4
Work mainly sedentary per cent of mothers	26.1	12.4
Mean development score of the place of residence	3.7	5.2

deaths 42.1 % were referred to the risk group by analysis B (the particular analysis developed for this group) and 38.4 per cent by analysis A.

Parallel analyses A 1 and B 1 were worked out for analyses A and B using the same control and risk groups while the number and content of the variables was different. 23 variables in the parallel analyses were identical, while A 1 and B 1 contained four variables not present in analyses A and B. The biological variables were identical apart from the number of children under 15. Two of four additional variables measured the mother's attitudes, the third how she felt about strenuousness of her own work and the fourth measured the father's vocational standing. Fig. 10 shows the distribution of the control and risk group cases in analyses B and B 1 by the probability classification of each of the two analyses. The diagrams illustrate the difference which the added number of variables makes in discriminant power. A study of the weighting of eigenvectors in Table 10 (page 23) revealed that a much smaller number of variables suffices to approach the effectiveness of the discriminant function of analysis B. The weighting of the four variables present only in analysis B 1 were low throughout, as were those of

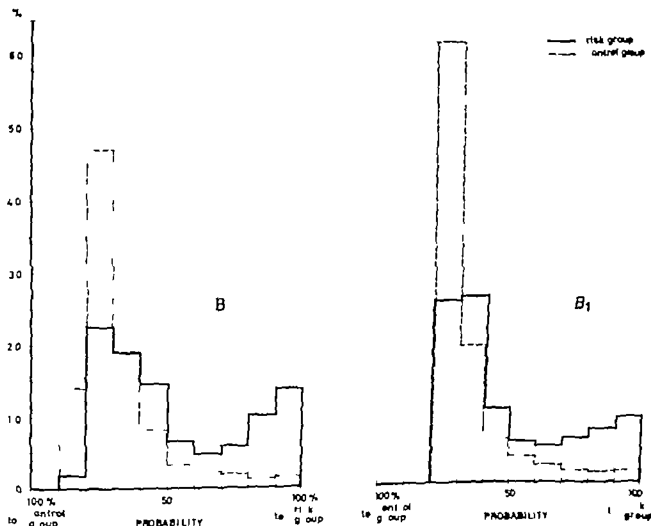


Fig. 10. Percentage distribution of the control and risk group cases on the basis of probability classification by discriminant function analyses B and B 1.

B is the analysis in which the two groups are controls and low birth weight infants who died (41 variables)
B 1 is the analysis with the same groups but 27 variables.

many variables included in both analyses. On the other hand, analysis B 1 lacked some variables with a relatively high weighting (14 26, 30, 33 36, 38 41 and 47).

In the parallel analyses the order of importance of the variables had undergone little change. Of the 15 variables with the best discriminant power in analyses A and B, 11 were present in analyses A 1 and B 1 In analysis A 1 eight of these were among the 11 with the best discriminant power and in analysis B 1 nine. In analysis A 1 the three variables of minor importance were distance from centres of population, internal migration, and character of the earlier place of residence, which were replaced by intellectual interest, father's occupation and mother's vocational standing. In analysis B 1 the variables distance from centres of population and is father a farmer were replaced by mother's vocational standing and intellectual interest.

The variables are presented in the following classified according to their contents Some were examined in detail by studying the distributions of the total number of cases. The variables selected for this examination were those whose influence on low birth weight and perinatal mortality had been less studied in earlier literature or for which the earlier results were ambiguous. This method at the same time provides a better picture of the nature of discriminant function analysis.

Biological characteristics Of the eight biological variables (1—8) used in the analysis, six proved essential in analyses of all low birth weight infants and four in those concerned with perinatal deaths of low birth weight infants, whereas in analysis C only age height and parity were among the variables with the best discriminant power Age of menarche has but little importance in all the analyses: higher age tends to increase the risk slightly When all the cases were classified into high risk and low risk groups by analysis A, the mean age of menarche in the high risk group was 14 years 2 months and in the low risk group 14 years 1 month. Previous perinatal deaths also proved of little importance in these analyses, whereas they had a high correlation to previous low birth weight infants. In analysis A, the high risk group showed perinatal deaths for 12.3 and the low risk group for 3.9 per cent of the mothers.

As mentioned earlier biological characteristics must also include the variables number of children under 15 and perhaps number of members in the household. As a whole, the biological variables played a very important role in the analyses. When the sum of the squares of weightings of variables 1—8 and 33 in each analysis was calculated, the result for analysis A was 0.629 analysis B 0.465 and analysis C 0.433 in other words, the biological variables obtained in analyses A, B and C 62.9 46.5 and 43.3 per cent, respectively of the total sum of squares of the weightings.

Social standing Of the variables of this group (9—16) the mother's marital status was the most important variable in all analyses concerned with low birth weight infants, while in analysis C it was of no importance. In most analyses, the social classification based on the mother's own occupation proved to possess a slightly better discriminant power than that based on the father's occupation.

Conditions during childhood The four variables describing the mother's childhood background (17—20) held a fairly central position in analysis C, whereas they played a minor role in the analyses concerned with low birth weight infants.

School attendance and intellectual interest This group contained two variables (21—22) of which one, the mother's school attendance, played a part only in analysis C. In the analyses concerned with low birth weight infants, intellectual interest, on average, had a better discriminant power than mother's school attendance.

Attitudes to pregnancy and support by public authorities The three variables of this group (23—25) had very little importance.

deaths 42.1 % were referred to the risk group by analysis B (the particular analysis developed for this group) and 38.4 per cent by analysis A.

Parallel analyses A 1 and B 1 were worked out for analyses A and B using the same control and risk groups while the number and content of the variables was different. 23 variables in the parallel analyses were identical, while A 1 and B 1 contained four variables not present in analyses A and B. The biological variables were identical apart from the number of children under 15. Two of four additional variables measured the mother's attitudes, the third how she felt about strenuousness of her own work and the fourth measured the father's vocational standing. Fig. 10 shows the distribution of the control and risk group cases in analyses B and B 1 by the probability classification of each of the two analyses. The diagrams illustrate the difference which the added number of variables makes in discriminant power. A study of the weighting of eigen vectors in Table 10 (page 23) revealed that a much smaller number of variables suffices to approach the effectiveness of the discriminant function of analysis B. The weighting of the four variables present only in analysis B 1 were low throughout as were those of

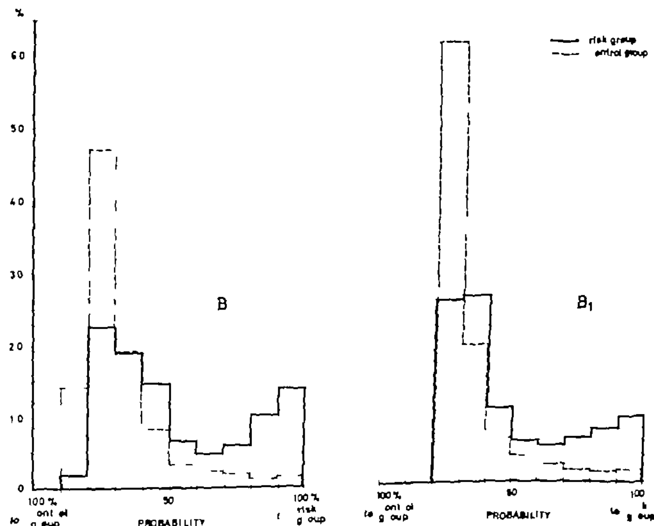


Fig. 10. Percentage distribution of the control and risk group cases on the basis of probability classification by discriminant function analyses B and B 1

B [illegible] (41 variables)
B 1 [illegible] 27 variables

birth weight infants they played a less pronounced part. In analyses of perinatal deaths, the absence of internal migration increased the risk. In analyses dealing with all low birth weight infants internal migration was important only in analysis A, whereas in A 1 this variable, though of low weighting, showed a reverse discriminant trend. For this reason, internal migration and present place of residence of all the cases of the series were cross-indexed, with mortality and low birth weight rates calculated on the basis of these variables. The results are presented in Tables 25 and 26. The difference in total mortality rates between those with no change of residence and others who had moved from one place to another was statistically almost significant. Table 25 presents the total mortality rates vis-à-vis the place of residence, the rate for urban dwellers being the lowest.

The differences in low birth weight rates between those of fixed residence and those who had moved from one place to another were small and of no statistical significance, although the rates of the former were slightly higher (Table 26). The differences according to the type of the current place of residence were also small. In analysis A, that of the low birth weight infants, the nature of the place of residence made no appreciable difference. The fact that internal migration in analysis A emerged as an important variable, increased mobility increasing the risk, was probably due to the variety of groups among the migrating population, the combination of variables selected for the analysis separating

TABLE 25 *Distribution of all cases by internal migration and nature of the current place of residence and the corresponding perinatal mortality rates*

Nature of current place of residence	No internal migration			Migrated			Migration not known			Total		
	Number of deaths	Total number	Mortality per 1,000	Number of deaths	Total number	Mortality per 1,000	Number of deaths	Total number	Mortality per 1,000	Number of deaths	Total number	Mortality per 1,000
Town	24	983	24.4	49	2,934	16.7	5	97	51.5	78	4,014	19.4
Large village or similar	26	928	28.0	60	2,281	26.3	1	33	30.3	87	3,242	26.8
Remote village	54	1,961	27.5	60	2,599	23.1	2	87	23.0	116	4,647	25.0
Not known	1	1	1000.0	1	3	333.3	0	24	0.0	2	28	71.4
Total	105	3,873	27.1	170	7,817	21.7	8	241	33.2	283	11,931	23.7

TABLE 26. *Distribution of all cases by internal migration and nature of the current place of residence and the corresponding low birth weight rates*

Nature of current place of residence	No internal migration			Migrated			Migration not known			Total		
	Birth weight under 2500 g, number	Total number of births	Low birth weight rate, per cent	Birth weight under 2500 g, number	Total number of births	Low birth weight rate, per cent	Birth weight under 2500 g, number	Total number of births	Low birth weight rate, per cent	Birth weight under 2500 g, number	Total number of births	Low birth weight rate, per cent
Town	41	983	4.2	120	2,934	4.1	11	97	11.3	172	4,014	4.3
Large village or similar	37	928	4.0	92	2,281	4.0	3	33	9.0	132	3,242	4.1
Remote village	86	1,961	4.4	105	2,599	4.0	3	87	3.4	194	4,647	4.2
Not known	1	1	100.0	0	3	0.0	0	24	0.0	1	28	3.6
Total	165	3,873	4.3	317	7,817	4.1	17	241	7.1	499	11,931	4.2

Mother's smoking The distribution of all cases by this variable (26) is presented in Table 24 with mortality rates for low birth weight infants and those with birth weights of 2500 g or more of smokers and non smokers. As can be seen from the table, mortality rates were lower in both weight groups if the mother had smoked than if she had not. In the birth weight group of 2500 g or more the difference was statistically significant The low birth weight rate among smokers was, however so much higher that the total mortality rates were the same for smokers and non-smokers. In the discriminant function analyses, smoking tended to be associated with the risk group in the two analyses concerned with low birth weight infants, and with control group in analysis C. 21 5 per cent of all the mothers of the series smoked 0 6 per cent smoked pipe, and they were combined with cigarette smokers. Of all mothers of low birth weight babies 32 1 per cent were smokers of the mothers of low birth weight infants whose baby died during the perinatal period 28 4 per cent smoked of all mothers giving birth to infants weighing 2500 g or more, 21 0 per cent were smokers and of the mothers of this birth weight class babies whose baby died during the perinatal period 12.7 per cent smoked

Work Variables 32 and 33 of this group (27—33) were discussed above among the biological variables. The remaining five were involved in the various analyses for a total of 16 times and two of the variables were important in two analyses the site of work in analysis B concerning deaths of low birth weight infants, and working posture in ana lysis C. No variable measuring the amount o work done was significant.

Housing standards These variables (34—37 were of some importance only in analysis I dealing with perinatal deaths of low birt weight infants where the number of room and running water were variables with moderate weighting

Standard of living Of the two variable of this group (38—39) car ownership was a important discriminant factor in analyses A and C, its weighting exceeding that of e.g mother s or father s occupation Ownership o a TV set had moderate weighting in analysis B

Internal migration and characteristics of the present and any possible earlier place of residence The variables of this group (40—47 proved to be important. Of these eight var iables, only distance from antenatal clinic and distance from neighbour were unimportant. Distance from medical officer had a high weighting in all analyses which contained this variable, increased distance increasing the risk

Low degree of industrialization of the place of residence and a remote place of residence increased the risk in analyses of perinatal deaths, while in those concerning all low

TABLE 24 *Distribution of all cases by mother s smoking habits Perinatal mortality rates for infants of smokers and non smokers separately for low birth weights and birth weights of 2500 g or more*

Mother smoking habits	Birth weight more than 2500 g			Birth weight 2500 g or less			Total number of cases		
	Total number	Number of deaths	Mortality per 1 000	Total number	Number of deaths	Mortality per 1,000	Total number	Number of deaths	Mortality per 1,000
Smokers	2,368	15	6.3	153	44	287 6	2,521	59	23 4
Non smokers	8,898	103	11.6	323	111	343.6	9,221	214	23.2
Not known	166	1	6.0	23	9	391.3	189	10	52.9
Total	11 432	119	10.4	499	164	328.7	11 931	283	23.7

Discussion

1 Material and method

The series of cases was collected from a district where public health facilities lag somewhat behind the general level of the country (162). In 1966 the total perinatal mortality rate in this district was 26.1 per thousand against 22.8 for the whole country (159). Internationally the public health facilities in the district are, however, on a relatively high level. In 1962, for example, the perinatal mortality in England and Wales was 30.8 per thousand (21) and in the United States 27.7 per thousand (156). Although the figures for different countries, owing to the varying definition of the perinatal period, are not fully comparable, the order of magnitude of the rate nevertheless gives an approximate idea (158).

The successful collection of information was essentially the result of the competent antenatal clinic network which has been operating in Finland for more than 20 years, and the small number of home deliveries. Information is lacking on only 4 per cent of the deliveries in the district during the period under review. This percentage may be assumed to represent largely the highest social bracket women who consult private practitioners, and the lowest social bracket women who carry their pregnancies without antenatal care. The results are as complete as such a study can reasonably be expected to attain, and since the sample contained deaths and low birth weight infants in the same proportions as the general population, the deficit does not significantly affect the results.

Of the data concerning the child, the birth weight and survival rate are highly reliable, whereas the accurate determination of gestational age presents a problem. The normal menstrual cycle varies, and defining the expected date of delivery as 280 days from the first day of the last menstrual period is only an approximation. For women whose menstrual cycle is irregular the exact determination of expected date *is difficult; furthermore,* with varying educational level and attendance, recollection of the first day of the last menstrual period is different. Selecting cases on the basis of these criteria would naturally result in a series in which the gestational age would be reliably indicated; such a series of cases would, however, be a selected series, both on social and on biological grounds (101, 102). Since *the present study was one* in which biological and social factors were of essential importance, and the purpose was not so much to determine distributions in social and biological optimum material as to analyse a series of mothers in whom these characteristics were the least favourable compared with the total population of a given geographical area, the study tried to reach a compromise between the accuracy of criteria and the number of the cases in which gestational age could be determined. As a result, the number of cases in which the gestational age was unknown, was very small, 3.3 per cent.

The fact that gestational age in a number of cases was determined as being 1—3 days shorter than it really was plays no part in individual cases since the shortening is smaller than the normal biological variation in the duration of gestation. But this deserves to be taken into account when the mean gestational lengths are studied; the effect of this shortening is of an order of 0.76 days (p. 16).

a group for which internal migration did increase the risk.

Distance from centres of population in the 43 variable analyses A B and C had moderate weighting the shorter the distance the greater the risk In analyses A 1 and B 1 this variable had a distinctly lower weighting Since the parallel analyses differed on several points, simple survey did not disclose the definite cause of this type of difference One possible explanation is, however that analyses A and B contained another variable which measured distance, viz. the distance from medical officer This combination of variables makes possible a more accurate localization of risk groups by distance since, in addition to geographical distance the developmental distance, and any other effect the place of residence may have, can also be measured

Discussion

1 Material and method

The series of cases was collected from a district where public health facilities lag somewhat behind the general level of the country (162). In 1966 the total perinatal mortality rate in this district was 26.1 per thousand against 22.8 for the whole country (159). Internationally the public health facilities in the district are, however, on a relatively high level. In 1962, for example, the perinatal mortality in England and Wales was 30.8 per thousand (21) and in the United States *27.7 per thousand* (156). Although the figures for different countries, owing to the varying definition of the perinatal period, are not fully comparable, the order of magnitude of the rate nevertheless gives an approximate idea (158).

The successful collection of information was essentially the result of the competent antenatal clinic network which has been operating in Finland for more than 20 years, and the small number of home deliveries. Information is lacking on only 4 per cent of the deliveries in the district during the period under review. This percentage may be assumed to represent largely the highest social bracket women who consult private practitioners, and the lowest social bracket women who carry their pregnancies without antenatal care. The results are as complete as such a study can reasonably be expected to attain, and since the sample contained deaths and low birth weight infants in the same proportions as the general population, the deficit does not significantly affect the results.

Of the data concerning the child, the birth weight and survival rate are highly reliable, whereas the accurate determination of gestational age presents a problem. The normal menstrual cycle varies, and defining the expected date of delivery as 280 days from the first day of the last menstrual period is only an approximation. For women whose menstrual cycle is irregular the exact determination of expected date is difficult. Furthermore, with varying educational level and attendance, recollection of the first day of the last menstrual period is different. Selecting cases on the basis of these criteria would naturally result in a series in which the gestational age would be reliably indicated; such a series of cases would, however, be a selected series, both on social and on biological grounds (101, 102). Since the present study was one in which biological and social factors were of essential importance, and the purpose was not so much to determine distributions in social and biological optimum material as to analyse a series of mothers in whom these characteristics were the least favourable compared with the total population of a given geographical area, the study tried to reach a compromise between the accuracy of criteria and the number of the cases in which gestational age could be determined. As a result, the number of cases in which the gestational age was unknown, was very small, 3.3 per cent.

The fact that gestational age in a number of cases was determined as being 1—3 days shorter than it really was plays no part in individual cases since the shortening is smaller than the normal biological variation in the duration of gestation. But this deserves to be taken into account when the mean gestational lengths are studied: the effect of this shortening is of an order of 0.76 days (p. 16).

The multi variable analysis chosen for the statistical treatment of the data, the discriminant function analysis was more practicable for the study than a factor analysis since it provides a possibility of classification and more practicable than the regression analysis since a probability classification does not require that the characteristic classified be measurable on a continuum

On the basis of the present results it is impossible to say whether better results could have been obtained using a battery of variables, all of which were normally distributed and continuous.

A study of groups with different degrees of risk based on probability classification provides the answers to the questions posed. Abernathy et al used a different modification of discriminant function analysis (the discriminant function was calculated via multiple regression and the groups were given fixed numerical values for the dependent variable) to find the factors discriminating between the survivals and the perinatal deaths (3) The variables included some of those used in the present study but also information on the course of pregnancy (blood pressure haemoglobin etc) and in some analyses the child s birth weight length at birth and gestational age were among the variables. For all these reasons, the results are not comparable The findings reported by Abernathy et al according to which the other variables do not essentially increase the discriminant power obtained from the child s birth weight length at birth and gestational age (3) is not particularly surprising the essential problem in perinatal mortality being low birth weight and low gestational age

The aim of a prospective study was well achieved The fact that the questionnaires concerning perinatal deaths of low birth weight infants were completed before delivery in only 70 per cent of the cases, does not seem to have affected the results.

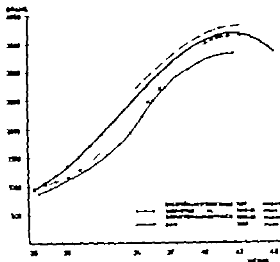
The method used for supplying the missing data gives an adequate correction as long as the true values of the missing data have the same distribution as the recorded data. If the assumption holds good that the reply has been omitted most often when it would have been in the negative then the existence of missing data increases classification bias for a few variables The most important individual variable of this type is the existence of previous low birth weight infants in analyses of low birth weight babies. Among the controls, this was the question most frequently left unanswered it was unanswered in 10.7 per cent of the cases Since in the group of control cases, 7 6 per cent of the recorded replies were in the affirmative this percentage of the missing replies is supplied in the affirmative. Should all missing replies in reality have been in the negative the false positive answers among a control population of 10 000 cases would have numbered 81.From the point of view of the total result, not even this possible classification error can be considered vital The discrimination of groups would of course be more complete if the recorded data were more complete

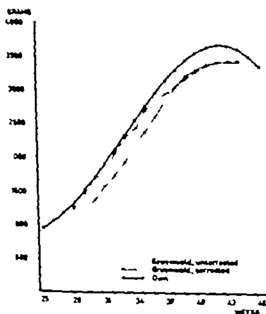
2 Variations in and correlations of birth weight and gestational age

The present results reveal the vast variations in birth weight even at identical gestational ages (Table 27 in Appendix 2) The variation has the relatively widest range in the early weeks of gestation a finding which agrees with that reported by other authors (14 45 62 77 102 141)

Of the 468 low birth weight infants in the present series of known gestational age 67 per cent were pre-term by their gestational age (Tables 2 and 3) The literature reports that 48—66 per cent of the low birth weight infants had a gestational age not exceeding 37 weeks (8 21 141 171) a percentage well in agreement with the present finding Although gestational age cannot be determined as accurately as birth weight, research

workers in this field today agree that even a child born at term may have a birth weight considerably below 2500 g. On the other hand some research workers express their doubts as to whether the relatively widest range of variation in birth weights in the early weeks of gestation is real. Gruenwald and Neligan have devoted particular attention to the problem (62, 102). In his studies of the birth weights of infants born in the 28th to 34th weeks of gestation, Gruenwald found that they showed a bimodal distribution (62) and Neligan in his series of cases arrived at the same result (102). They combined this finding with the clinical observation that many women, in early pregnancy had bleeding which may have been misinterpreted as the last menstrual period before pregnancy. The gestational age of babies born would therefore in reality be higher than the calculated age. On this basis, Gruenwald corrected his intrauterine growth curve by deleting up to the 34th week of gestation the lower peak which represented the higher weight class in bimodal distribution and correcting the 34th to 37th week interval by extrapolation from the values at the beginning and end of the curve. Fig. 11 shows Gruenwald's corrected and uncorrected intrauterine growth curves together with the curve concerning the present series of cases.


Fig. 12 The 50th percentile intrauterine growth curve based on the present findings, together with curves by a few other authors.


Fig. 11 The 50th percentile intrauterine growth curve of the present series of cases together with Gruenwald's corrected and uncorrected curves.

The best method of calculating the values of the growth curve is naturally extremely difficult to decide. The intrauterine growth curve based on birth weights of pre-term infants by no means represents a normal foetal population, since prematurity in itself is a nonphysiological condition (47, 134, 136); this does not, however, prevent studies of pathological conditions. But this means that the distribution of the birth weight for pre-term babies may include a larger proportion of extreme values compared with the intrauterine weight of unborn babies. The bimodal distribution of birth weights at the early weeks of gestation found by Gruenwald and Neligan would be replaced by a unimodal distribution if the intrauterine weight of term babies could be measured at that time.

Fig. 12 presents a number of intrauterine growth curves reported by various authors,

together with the curve based on the present series The curve of Lubchenco et al. (86) is well known it is based on data collected at a Colorado Hospital a place 5 000 feet above sea level In addition stillbirths and infants with severe deformities had been removed from the series, as had infants considered too large for their gestational age. Most of these factors would tend to flatten the curve. The other two curves on the diagram have been published in national publication series for practical pediatrics but they are of interest here as one is based on Swedish and the other on Finnish data. Engström and Sterky s initial series covers some 85 per cent of all births in Sweden during one year but the criteria laid down for both maternal and foetal illnesses and for calculation of gestational week have caused so many deletions that the growth curve is really based on only just over 60 per cent of the initial series (38) Since the growth curve values of Fig. 12 were taken for the present work from a drawing they may not be exact. The curve in the figure is the boys curve the curve for girls had a course very similar to that based on the present series. In addition to that of Engström and Sterky there is just another Swedish intrauterine growth curve which after the 38th week runs a higher course than the present curve (83) Prior to the 36th week of gestation birth weights reported by Karn and Penrose (77) Taback (141) Fraccaro (45) and Neligan (102) exceeded those based on the present series.

The differences between the intrauterine growth curve by Bäckström and Kauppinen (24) and the present curve are interesting, since the former is based on Helsinki mothers — all urban dwellers — while only one-third of the present series lived in towns. Term births in the series by Backström and Kauppinen had somewhat lower birth weights but since the parity distribution of the mothers was very probably different, it seems that had parity been fixed the birth weights of Helsinki babies would be equal to or slightly higher than those of the present series. The differences, however were considerably more pronounced from the 28th to the 37th week of gestation This may of course be partly due to the different mathematical treatment of data, but there is no proof that the etiology of pre-term births might not show geographical differences affecting intrauterine growth rates.

The higher mean birth weight of boys is well known and visible in all series. In the present data the mean birth weight of boys exceeded that of girls by 118 grams. The shorter duration of boy pregnancies is apparent in many reports (45, 77 148) in the present series it was, on average, 1 1 days shorter than that of girl pregnancies (page 16)

The boy/girl ratio of the total number of cases is unusually high 1086/1000 In an international survey covering seven countries and all births over 15 years, the highest ratio 1079 applied to Sweden in 1956 (158) According to the paper in countries with a high boy/girl ratio such as Sweden and the Netherlands, perinatal mortality rate is low Some authors have associated the high boy/girl ratio with a cold climate, claiming that more boys were conceived in the cold season (111) Timonen, in his studies covering the years 1957—58 found that the boy/girl ratio in North Finland was statistically significantly higher than in South Finland (149). The boy/girl ratio 1150 from Korea reported by Kang and Cho ranks among the highest in the literature (76) The higher proportion of boys among the cases is, from the overall point of view sufficiently negligible not to affect the mean birth weight or gestational age.

3 Perinatal mortality rate correlated with birth weight and gestational age

The correlation between the perinatal mortality rate and birth weight (Table 28 in

Appendix 3 Fig. 5) is parallel to that reported in earlier population studies (14 39): the mortality rate falls steeply from the lowest towards the higher weight groups but increases again slightly in the highest weight groups. Studied by 200 gram weight groups, the mortality rate was lowest between 3500—3699 grams by the customary 500 gram weight groups it was lowest between 3500—3999 grams (4 9 per thousand). The weight group with the lowest mortality therefore, is only slightly abo e the mean birth weight of all the cases, 3440 grams, and coincides *with the most frequent* weight groups. In these weight groups, the mortality rate is thus only about one-fifth to one-seventh of that of all the cases. If gestational age *is simultaneously taken into account*, the mortality rate of the most favourable group is only about one-tenth of that of all the cases, although such a group covers a good *40 per cent of the cases (115). In studies of* neonatal mortality the weight group representing the lowest mortality rate has usually been well above the mean birth weight level *(45 77 131), but as a rule the most favour*able weight group has been the same as in the present study and the difference is due to the lower mean birth weight of the other *reports.*

The correlation of perinatal mortality with gestational age also corresponds to the earlier population studies (14 39). In the present study the mortality rate was lowest in the 40th week of gestation, which is compatible with other authors results.

When the *risk* of perinatal death is reviewed two-dimensionally in relation both to birth weight and gestational age (Table 7), there are certain differences from a similar study by Butler (22). He studied *only cases from* 36 (full) weeks of gestation onwards, using standard deviations instead of percentiles. The results are parallel in that the mortality *rate* is lowest above the *curve representing the* mean birth weight, in the present study between 50—90 percentiles and in Butler's study between standard deviations of 0— +2, rising steeply below this range. Butler also reports, however a definite rise in mortality roughly double, when +2 SD is surpassed, while in the present survey mortality in the over 90 percentile range rose only in the pre-term group. This difference may be explicable because +2 SD weighs more heavily against extreme cases than the 90th percentile, and corresponds to about the 98th percentile. *In that case the difference, however might* also be expected to be larger among infants below —2 SD but Butler's mortality rate 68.5 per thousand under —2 SD is very close to the combined mortality rate for term and post-term babies of the *present series*, which was 61.7 per thousand. The finding can be explained from the different overall mortality rates of the two series for the British series, collected 8 years earlier *it was 33.. per thousand against 23.7 per* thousand for the present survey Other authors have found that a fall in perinatal mortality rates in recent years was concerned *mainly with infants of birth weights exceed*ing 2500 grams (13 29). This finding, when applied to the problem under discussion, suggests that the mortality of babies below *the standard deviation range has not changed*, while that above this range shows differences which depend on when the cases were collected. In the range of 50—90 percentiles *the* mortality of term and post-term babies [illegible] the present study was 5.6 per thousand, while in the British study within the range 0 — —1 SD it was 7.3 and within the range +1 — —[illegible] SD it was 8.6 per thousand, [illegible] about 40 per cent higher [illegible] in the present study [illegible] for births below the [illegible] only 11 per cent [illegible] which [illegible] small for [illegible] roughly [illegible] [illegible]

[illegible]

trauterine growth curves cannot, however be disregarded. Butler was unable to determine the gestational length in 13 per cent of his cases while the birth weight was unknown in 5 per cent In the present study the 3 per cent whose gestational length was unknown had both a mortality rate and low birth weight rate twice that of the total number of cases, and on this basis some group might be assumed to be over represented among the cases falling outside the investigation A more important difference however is that Butler excluded all macerated stillbirths and major congenital anomalies which clearly influenced weight for given gestation In Butler's series macerated stillbirths accounted for some 30 per cent of all deaths and some 50 per cent of all stillbirths (21) Exclusion of these cases was naturally due to the fact that autolysis is associated with weight loss in the course of time and when efforts were made to obtain the most accurate results possible such cases were excluded For the relative distribution of perinatal mortality over the intrauterine growth curve this naturally makes no difference unless stillbirths are associated with biological factors producing intrauterine weight increase different from that of later deaths. There is reason to assume, however that placental insufficiency is more frequent among the stillbirths than the others (58 60) and on this basis the birth weights of this group would differ from those of the others Hence Butler's series would exclude a relatively higher proportion of perinatal deaths located below the mean intrauterine growth curve

In the present study the interest is focused on intrauterine growth which falls below the normal level and the accompanying increased perinatal mortality For this reason a large number of the stillbirths could not be excluded from the analysis. The weight loss during autolysis is probably restricted to a few hundreds of grams whenever the rule of obstetric treatment in cases of foetal death is to induce labour as soon as possible, whereas the total distribution in birth weights in most groups of gestational length is several thousands of grams.

Table 9 reviews the mean birth weights of infants who died in different phases of the perinatal period with especial regard to the weight loss during autolysis of stillbirths. Deaths during delivery were combined with neonatal deaths, since hardly any measurable weight loss has time to occur The study of British Perinatal Mortality recorded maceration in 13 per cent of the deaths during delivery but maceration alone does not imply weight loss. It is impossible to say to what extent the lower mean weight of babies who died before the start of delivery compared with those who died later was a result of weight loss during autolysis and to what extent it was due to other causes of death apparently there was a combination of both groups of causes. Table 9 reveals, however that all perinatal deaths were markedly smaller for their gestational age than the survivals. As can be seen from Fig. 7 the inclusion of foetal deaths did not appreciably affect the values of the 50th percentile of the intrauterine growth curve, but it is probable that exclusion of these cases would imply a changed distribution of perinatal mortality over the different areas of the intrauterine growth curve.

The higher perinatal mortality of pre-term high birth weight infants has been reported earlier (14 16) As already mentioned, the true gestational age of these babies was discussed by Gruenwald and Neligan Increased mortality may naturally be taken to indicate that these infants really were pre-term births and that the increased mortality was due to prematurity Another explanation as advanced by Battaglia is that the gestational length in these cases may have been incorrectly estimated owing to a bleeding during pregnancy and that this bleeding would at the same time have injured the foetus, causing increased perinatal mortality (14)

4 Perinatal mortality and birth weight correlated to maternal biological characteristics and socio-economic circumstances and prediction of the former from the latter

a. *The child's characteristics in identified risk groups*

The mean values of the birth weights and lengths at birth of low risk and high risk groups formed on the basis of the probability classification of analysis A, which dealt with *all low birth weight infants*, can be compared with the corresponding mean values of the total or partial populations of different countries. The birth weight 2970 g and length 48 1 cm of the highest risk group 4 (Table 16) agree w th those reported by Ghosh from India in 1959—61 2720 g and 48.3 cm, respectively (51) Ghosh s series did not contain stillbirths, but its neonatal mortality was 35 per thousand. Since stillbirths usually equal about half the perinatal mortality (Table 1), the perinatal mortality rate of 72.4 per thousand of the risk group (Table 15) also agrees with the Indian series. The low b rth weight rate in the present risk group was 22.0 per cent and in the Indian series 24.2 per cent (52).

In the *next highest* risk group 3 the mean birth weight was 3180 g and perinatal mortality 44 1 per thousand. In 1962 the mean birth weight of U.S. Negro children was 3140 g (155) and perinatal mortality 56.2 per thousand (156). The low birth weight rate in risk group 3 was 9.2 per cent and among U.S. Negroes 13 1 per cent (155).

The low risk *group* 2 agrees best with the mean alues of the present series. The low risk group 1 with a mean birth weight of 3544 g and length at birth of 50.6 cm, corresponds to the Swedish series of 1956—57 published by Engström and Sterky with a mean birth weight of 3500 g and length at birth of 50 9 cm (38) The perinatal mortality rate in Sweden in 1965 was 19.6 per thousand (113), and that of group 1 16.2 per thousand. The low *birth weight* rate in Sweden is, *however* around 5 per cent (158), whereas in the present group 1 it was 1 9 per cent. No geographical population corresponding to the mean birth weight — 3770 grams — of the minimum risk subgroup separated within the low risk group 1 has been reported anywhere.

Although the battery of variables used in the discriminant function analysis assembled in the high risk groups a *few* characteristics, e.g. the low parity not typical of the Indian or the U.S. Negro parturient populations serving for comparison, the high risk groups of the present series differed on many of the variables used from the total series in the same direction as the control populations e.g. from the Swedish series.

It is interesting that the birth weights and lengths at birth, and perinatal mortality rates, in the compared studies agreed relatively well, *but in a natural population the low birth* weight rate does not fall as low as in the lowest risk group

The literature reports several studies on the differences in mean birth weights and low birth weight rates between the children of populations of two or more races living in the same geographical area (15 31 39 68 71 126, 127 174) A general finding is that *the races in which children s mean birth* weights are lower live in poorer socio-economic circumstances.

The part played by genetics in determining birth weight and length at birth has been examined by twin studies, studies of consanguineous parents, and comparisons of sister sister and brother-brother pairs (47 50 97 98). Even though the foetal genotype does affect the size of the infants born, it seems that only a minor *proportion* of the total variance of birth weights is determined genetically while a considerably higher *propor*

tion is governed by the parents socio-economic circumstances and actual biological status

When the differences in mean birth weights between the high risk and low risk groups in different gestational weeks are compared in Table 20 and Fig 9 with the corresponding differences between girls and boys in Table 6 the differences between risk groups are found to exceed those between girls and boys. The difference in mean birth weights between risk groups is 366 g, while that between girls and boys is 118 g The birth weights of the low risk group are higher from the 29th—30th gestational weeks whereas the birth weight of boys exceeds that of girls regularly only from the 33rd—34th gestational week onwards

The difference in intrauterine growth rate between high risk and low risk groups was thus demonstrable from the 29th—30th gestational week onwards. This finding differs from Gruenwald's assumption according to which differences in birth weights due to various causative factors — chronic foetal distress, maternal diabetes, twin pregnancy or racial (probably economic and nutritional) factors — do not emerge with statistical significance before the 34th gestational week (61)

When the theory suggesting that the duration of gestation of high birth weight — low gestational age infants might have been miscalculated is reviewed in this connection it seems hardly probable that the mothers of the low risk group who on average have a better social standing would report the date of their last menstrual period less accurately On this basis it may be assumed that the intrauterine growth curves of different parturient populations in the early gestational weeks really are different. Were the cases more numerous and had the multi variable analysis been designed to discriminate the growth retarded infants, the differences might perhaps be visible even earlier In the present study the high risk group was not composed exclusively of infants small for their calculated term, as can be seen from Table 19 Ounsted studied the characteristics of mothers of growth retarded infants and came to the conclusion that low birth weight infants born after short gestation with average birth weights in view of their gestational age constitute an entirely different biological group from those low birth weight infants whose intrauterine growth was retarded (104) The mothers of the latter group according to Ounsted, were likely to give birth again to a similar infant, whereas the low birth weight representing the average intrauterine growth phase lacked this likelihood of recurrence.

When the intrauterine growth rates of Helsinki and North Finnish infants are re-examined against the above background (Fig. 12), one may speculate whether or not the low birth weight infants of the Helsinki population of mothers contained relatively more with retarded growth than those of North Finland. In a population of mothers with a high mean parity in which family planning has not yet been generally accepted, pathologic groups representing high birth weights, such as maternal diabetes and Rhesus incompatibility may assume a dominant position compared with the relative number of low birth weight infants

The high risk group contained statistically significantly fewer boys than the initial series the boy/girl ratio for the former was 910 and for the latter 1086 per thousand All series of low birth weight infants with the group limit set at a given birth weight unfailingly contain more girls since the mean birth weight of girls is lower The variables used to classify a number of the present cases into risk group had nothing to do with the child's birth weight but concerned maternal characteristics, for which reason the explanation must be sought elsewhere Ounsted when examining infants of retarded intrauterine growth looked into whether their mothers were disposed to bearing a higher proportion of girls than the normal distribution presupposed (104) She also examined infants of

above-average intrauterine growth and tried to discover whether their disposition to have more boys than girls differed from the normal distribution (105) She was unable to *prove* such a disposition in either case. The present finding that high risk groups contained fewer boys may of course have its explanation in that, for some reason or other abortions are more frequent in boy than girl pregnancies.

b Importance of maternal characteristics in different risk groups

The mother s *parity* is known to be posit ely correlated with the birth weight of the expected child (45 72, 77 127 148 149 157) whereas correlation between gestational length and parity is low (45 82, 148, 149). Karn and Penrose found that gestational length was slightly less in the higher parity groups (77) In the present study low parity also tended to increase the risk in analyses in which the discriminated group was composed of all low birth weight infants.

If the risk of perinatal mortality is shown on a curve against parity the curve will be U-shaped. The risk is highest for primiparas and increases again from parity 4 upwards (21 34 40, 64 72, 93). In analyses with perinatal mortality cases functioning as the groups to be separated, parity has a moderate weighting, low parity tending to increase the risk. In analysis B however high parity increased the risk. The ariable number of children under 15 which also partly covers the concept of parity in this analysis increased the risk when the number of children under 15 was low

The positive correlation between *maternal age* and perinatal mortality is also a known fact (21 34 40 64 72, 93). Mortality has been found to increase with age especially after the age of 35 (21 34) Feldstein, with a binary ariable multiple regression analysis, studied the effect of maternal age on perinatal morta lity (41). He found that the perinatal morta lity rate for mothers aged under 20 was 6.7 per cent higher than that for the whole series, but after the effect of parity and socio-economic circumstances was eliminated the *mortality* was 11.8 per cent below the mean value. The risk of perinatal mortal ity was smallest if the mother was 20—24 years old, after the elimination of the effect of parity and social group With mothers aged 25—29 years, favourable parity and social group usually reduced the risk, but after these factors were eliminated the risk was higher than among those under 20 years of age. For mothers aged 40 years or more the elimination of other factors had little effect on the risk of perinatal mortality and the risk was twice that of the middle of the series. With primiparas, favourable age could usually be taken to reduce the risk resulting from their parity rating.

In the present study advancing age, in all analyses, both those concerned with birth weight and with perinatal mortality tended to increase the risk. This variable was relatively of the greatest importance in the analysis concerning perinatal deaths with birth weights of 2500 g or more.

The correlation of maternal *height* with the infant s birth weight has been studied by many authors, and the correlation has been positive (10 17 25 75 84 92, 143 144 146) In the present study a mother s shorter stature increased the risk of low birth weight infants and of perinatal mortality Earlier authors also found that infants of short mothers had a higher perinatal mortality rate (21 75 146). Adult height is considered to be the combined result of the individual s genotype and socio-economic environment during childhood, in that genes determine the potential height while actual height depends largely on nutri tion, health, etc. during the period of growth besides genes (21 23 70, 79 142)

The mother s *weight* is not a constant like height, but reflects her size, structure and her nutritional condition, and in extreme cases disease. In the present study the mother s weight was more important in analyses A

and A 1 concerned with all low birth weight infants than her height, a low weight tending to increase the risk while in the analyses of perinatal deaths height had a higher weighting than body weight. Love and Kinch found in their study that mother's weight before pregnancy was better correlated with the child's birth weight than maternal height (84) Many authors have found that mothers of lighter weight had children of lower birth weights (9 146 149 150) On the other hand obesity has been found to increase the low birth weight rate (42)

The correlation of maternal weight with perinatal mortality is less obvious. In the discriminant function analysis reported by Abernathy et al. increasing weight suggested increased perinatal mortality rate (3) while Kaltreider failed to trace any correlation between perinatal mortality and maternal weight (75) Sauramo studied abnormally high and low weights among Finnish mothers, and found that the foetal mortality rate among the obese was greater (128) Fisher and Frey by contrast noted no increase in the foetal mortality rate among over weight mothers (43)

Menarche age is correlated to the socio-economic environment in that the age of menarche in better socio-economic circumstances is lower (135) on the other hand age of menarche has been found to have correlations, interpreted as genetic, in mother–daughter and sister sister pairs (50) In the present study the age of menarche did not discriminate between the controls and the groups to be separated.

Previous abortions had a moderate weighting in all those discriminant function analyses in which low birth weight infants were the group to be separated The result was parallel to those of earlier studies (20 21 49 138)

Previous low birth weight infants is the variable with the highest or second highest weighting in all discriminant function analyses of low birth weight infants, whereas in that of perinatal deaths with birth weights of 2500 g or more this variable had no appreciable importance. Earlier authors have also found this variable to increase the risk of low birth weight and perinatal mortality (20 21 49 11, 104 167) In Ounsted's study the risk of bearing a second or further infant of low birth weight was increased when low birth weight was the result of intra uterine nutrition but not when it was due to premature delivery (104)

Previous perinatal mortality did not indicate increased risk in any of the present analyses. Since previous perinatal mortality is markedly correlated with previous low birth weight infants, the distribution of this variable, too was different in the high risk and low risk groups of analysis A In the British perinatal mortality study the correlation of previous perinatal mortality with the present mortality was more pronounced than that of previous low birth weight infants and previous abortions (21)

The number of children under 15 is a variable which covers both parity interval between pregnancies and number of children who had died before the age of 15 As pointed out before the question is phrased so that it includes, wherever mothers live in extended-family households, children other than the mother's own Component factors are known to exert a parallel effect the expected child's prognosis is made worse by low parity as shown above (p 47) long intervals between pregnancies (163) and deaths of earlier children It is also possible that the sphere of life associated with extended family households tends to reduce the risk. Infant mortality is known to be much more closely connected with socio-economic circumstances than is perinatal mortality (154 158) It is possible that the poor discriminant power of perinatal mortality in the combinations of variables used compared with the variable subsuming the whole childhood mortality rate, can be explained against this backround

In the present study *illegitimacy* was a risk increasing factor in all analyses except that

ealing with perinatal deaths with birth weight of 2500 g or more. The finding was contrary to that reported from Great Britain where the perinatal mortality rate of illegitimate children was clearly higher for even this birth weight group (21). In the same study the low birth weight rate among illegitimate children was also higher. In many other countries illegitimacy has been found to increase perinatal mortality for example in Denmark (158) and in Finland too similar results have previously been reported (7 109). Society in general, has become more tolerant towards illegitimacy and it is possible that the widely differing percentages of unmarried mothers in different countries reflect different attitudes to the issue. In Sweden the percentage of unmarried mothers, 13 per cent in 1964 is considerably higher than in many countries (158), and it is interesting to see how changed attitudes will be reflected in the prognosis of children born out of wedlock. Parmelee found from his studies that unmarried mothers, whose antenatal care was well organized, had the same low birth weight rates as the total population (107).

In the present study *social and economic standing* was analysed by means of a large number of variables (Table 10). Variables classified to indicate social status, housing level and standard of living are here discussed together since on the basis of the present results they cannot be considered to possess any importance as groups. The second best discriminant factor after marital status is *ownership of ca*. According to West, in Finnish rural communes automobile density is growing faster than the economical variables upon which it depends (164). According to the present study too, car ownership appears to be a more dynamic variable than e.g. the mother's or father's social class.

With the combination of variables used in the present study social classification based on the *mother's occupation* seemed to possess, on average, a slightly better discriminant power than that based on the *father's occupation*.

Irrespective of how the socio-economic level was measured, its low level tends to increase the risk of both low birth weight and perinatal mortality. Authors in different parts of the world have arrived at parallel results on this point (10—12, 15 18 21 35 54 71 72 110 117 119 126, 132, 133 145 147 163 165 166). In the present study economic factors increased the risk of perinatal deaths of low birth weight infants. This finding was contradictory to that reported by Ahvenainen and Kunnas in their study of hospital cases the neonatal mortality of low birth weight infants was slightly higher for the higher social class infants (7). When these studies are compared it should be borne in mind that the present series also included prenatal deaths, and that there may be differences between the social classes as regards readiness to seek medical advice for children.

Variables illustrating the *circumstances during childhood* were more important in the analysis concerned with perinatal deaths of infants with birth weights of 2500 g or more than in the other analyses. The most prominent discriminant factor increasing the risk was small *number of mother's siblings* a *finding contradictory to that of the British* study according to which perinatal mortality rate increased in direct proportion to the number of mother's siblings and was visible in all social classes (79). Within the framework of the present study it cannot be said whether size of family as a risk increasing factor should be associated with the relatively high degree of segregation of the population living in the region studied, with the consequence that there might be an increased incidence of conditions due to the meeting up of harmful recessive genes, but this possibility does exist.

Social classification based on the occupation of the child's parents was more important in the present study than that based on the *occupation of the child's maternal grandfather*. *The finding* is contradictory to that reported

and A 1 concerned with all low birth weight infants than her height, a low weight tending to increase the risk while in the analyses of perinatal deaths height had a higher weighting than body weight. Love and Kinch found in their study that mother's weight before pregnancy was better correlated with the child's birth weight than maternal height (84) Many authors have found that mothers of lighter weight had children of lower birth weights (9 146, 149 150) On the other hand obesity has been found to increase the low birth weight rate (42)

The correlation of maternal weight with perinatal mortality is less obvious. In the discriminant function analysis reported by Abernathy et al., increasing weight suggested increased perinatal mortality rate (3) while Kaltreider failed to trace any correlation between perinatal mortality and maternal weight (75) Sauramo studied abnormally high and low weights among Finnish mothers, and found that the foetal mortality rate among the obese was greater (128) Fisher and Frey by contrast, noted no increase in the foetal mortality rate among over weight mothers (43)

Menarche age is correlated to the socio-economic environment in that the age of menarche in better socio-economic circumstances is lower (135) on the other hand, age of menarche has been found to have correlations, interpreted as genetic, in mother-daughter and sister sister pairs (50) In the present study the age of menarche did not discriminate between the controls and the groups to be separated

Previous abortions had a moderate weighting in all those discriminant function analyses in which low birth weight infants were the group to be separated. The result was parallel to those of earlier studies (20 21 49 138)

Previous low birth weight infants is the variable with the highest or second highest weighting in all discriminant function analyses of low birth weight infants whereas in that of perinatal deaths with birth weights of 2500 g or more this variable had no appreciable importance. Earlier authors have also found this variable to increase the risk of low birth weight and perinatal mortality (20 21 49 88, 104 167) In Ounsted's study the risk of bearing a second or further infant of low birth weight was increased when low birth weight was the result of intra-uterine nutrition but not when it was due to premature delivery (104)

Previous perinatal mortality did not indicate increased risk in any of the present analyses. Since previous perinatal mortality is markedly correlated with previous low birth weight infants, the distribution of this variable, too was different in the high risk and low risk groups of analysis A. In the British perinatal mortality study the correlation of previous perinatal mortality with the present mortality was more pronounced than that of previous low birth weight infants and previous abortions (21)

The number of children under 15 is a variable which covers both parity interval between pregnancies, and number of children who had died before the age of 15 As pointed out before the question is phrased so that it includes, wherever mothers live in extended family households, children other than the mother's own Component factors are known to exert a parallel effect the expected child's prognosis is made worse by low parity as shown above (p 47) long intervals between pregnancies (163) and deaths of earlier children It is also possible that the sphere of life associated with extended family households tends to reduce the risk. Infant mortality is known to be much more closely connected with socio-economic circumstances than is perinatal mortality (154 158) It is possible that the poor discriminant power of perinatal mortality in the combinations of variables used, compared with the variable subsuming the whole childhood mortality rate can be explained against this backround

In the present study *illegitimacy* was a risk increasing factor in all analyses except that

dealing with perinatal deaths with birth weight of 2500 g or more. The finding was contrary to that reported from Great Britain where the perinatal mortality rate of illegitimate children was clearly higher for even this birth weight group (21). In the same study the low birth weight rate among illegitimate children was also higher In many other countries illegitimacy has been found to increase perinatal mortality for example in Denmark (158), and in Finland too similar results have previously been reported (7 109) Society in general, has become more tolerant towards illegitimacy and it is possible that the widely differing percentages of unmarried mothers in different countries reflect different attitudes to the issue. In Sweden the percentage of unmarried mothers, 13 per cent in 1964 is considerably higher than in many countries (158), and it is interesting to see how changed attitudes will be reflected in the prognosis of children born out of wedlock. Parmelee found from his studies that unmarried mothers, whose antenatal care was well organized, had the same low birth weight rates as the total population (107)

In the present study *social and economic standing* was analysed by means of a large number of variables (Table 10) Variables classified to indicate social status, housing level and standard of living are here discussed together since on the basis of the present results they cannot be considered to possess any importance as groups. The second best discriminant factor after marital status is *ownership of car* According to West, in Finnish rural communes automobile density is growing faster than the economical variables upon which it depends (164) According to the present study too, car ownership appears to be a more dynamic variable than e.g. the mother s or father's social class.

With the combination of variables used in the present study social classification based on the *mother s occupation* seemed to possess, on average, a slightly better discriminant power than that based on the *father s occupation*

Irrespective of how the socio-economic level was measured, its low level tends to increase the risk of both low birth weight and perinatal mortality Authors in different parts of the world have arrived at parallel results on this point (10—12, 15 18 1 35 54 71 72, 110 117 119 126, 132, 133 145 147 163 165 166). In the present study economic factors increased the risk of perinatal deaths of low birth weight infants. This finding was contradictory to that reported by Ahvenainen and Kunnas in their study of hospital cases the neonatal mortality of low birth weight infants was slightly higher for the higher social class infants (7). When these studies are compared it should be borne in mind that the present series also included prenatal deaths, and that there may be differences between the social classes as regards readiness to seek medical advice for children.

Variables illustrating the *circumstances during childhood* were more important in the analysis concerned with perinatal deaths of infants with birth weights of 2500 g or more than in the other analyses. The most prominent discriminant factor increasing the risk was small *number of mother s siblings* a finding contradictory to that of the British study according to which perinatal mortality rate increased in direct proportion to the number of mother s siblings and was visible in all social classes (79). Within the framework of the present study t cannot be said whether size of family as a risk increasing factor should be associated with the relatively high degree of segregation of the population living in the region studied, with the consequence that there might be an increased incidence of conditions due to the meeting up of harmful recessive genes, but this possibility does exist.

Social classification based on the occupation of the child s parents was more important in the present study than that based on the *occupation of the child's maternal grandfather* The finding is contradictory to that reported

and A 1 concerned with all low birth weight infants than her height, a low weight tending to increase the risk while in the analyses of perinatal deaths height had a higher weighting than body weight. Love and Kinch found in their study that mother's weight before pregnancy was better correlated with the child's birth weight than maternal height (84) Many authors have found that mothers of lighter weight had children of lower birth weights (9 146 149 150) On the other hand obesity has been found to increase the low birth weight rate (42)

The correlation of maternal weight with perinatal mortality is less obvious. In the discriminant function analysis reported by Abernathy et al. increasing weight suggested increased perinatal mortality rate (3) while Kaltreider failed to trace any correlation between perinatal mortality and maternal weight (75) Sauramo studied abnormally high and low weights among Finnish mothers, and found that the foetal mortality rate among the obese was greater (128) Fisher and Frey by contrast, noted no increase in the foetal mortality rate among over weight mothers (43)

Menarche age is correlated to the socio-economic environment in that the age of menarche in better socio-economic circumstances is lower (135) on the other hand age of menarche has been found to have correlations, interpreted as genetic, in mother-daughter and sister sister pairs (50) In the present study the age of menarche did not discriminate between the controls and the groups to be separated.

Previous abortions had a moderate weighting in all those discriminant function analyses in which low birth weight infants were the group to be separated The result was parallel to those of earlier studies (20 21 49 138)

Previous low birth weight infants is the variable with the highest or second highest weighting in all discriminant function analyses of low birth weight infants whereas in that of perinatal deaths with birth weights of 2500 g or more this variable had no appreciable importance Earlier authors have also found this variable to increase the risk of low birth weight and perinatal mortality (20 21 49 88 104 167) In Ounsted's study the risk of bearing a second or further infant of low birth weight was increased when low birth weight was the result of intra uterine nutrition but *not* when it was due to premature delivery (104)

Previous perinatal mortality did not indicate increased risk in any of the present analyses. Since previous perinatal mortality is markedly correlated with previous low birth weight infants, the distribution of this variable, too was different in the high risk and low risk groups of analysis A. In the British perinatal mortality study the correlation of *previous perinatal mortality* with the present mortality was more pronounced *than that of* previous low birth weight *infants and* previous abortions (21)

The number of children under 15 is a variable which covers both parity interval between pregnancies, and number of children who had died before the age of 15 As pointed out before, the question is phrased so that it includes, wherever mothers live in extended family households, children other than the mother's own Component factors are known to exert a parallel effect the expected child's prognosis is made worse by low parity as shown above (p 47) long intervals between pregnancies (163) and deaths of earlier children It is also possible that the sphere of life associated with extended family households tends to reduce the risk Infant mortality is known to be much more closely connected with socio-economic circumstances than is perinatal mortality (154 158) It is possible that the poor discriminant power of perinatal mortality in the combinations of variables used compared with the variable subsuming the whole childhood mortality rate can be explained against this backround

In the present study *illegitimacy* was a risk increasing factor in all analyses except that

dealing with perinatal deaths with birth weight of 2500 g or more. The finding was contrary to that reported from Great Britain where the perinatal mortality rate of illegitimate children was clearly higher for even this birth weight group (21). In the same study the low birth weight rate among illegitimate children was also higher. In many other countries illegitimacy has been found to increase perinatal mortality, for example in Denmark (158), and in Finland too similar results have previously been reported (7, 109). Society in general, has become more tolerant towards illegitimacy and it is possible that the widely differing percentages of unmarried mothers in different countries reflect different attitudes to the issue. In Sweden the percentage of unmarried mothers, 13 per cent in 1964, is considerably higher than in many countries (158), and it is interesting to see how changed attitudes will be reflected in the prognosis of children born out of wedlock. Parmelee found from his studies that unmarried mothers, whose antenatal care was well organized, had the same low birth weight rates as the total population (107).

In the present study *social and economic standing* was analysed by means of a large number of variables (Table 10). Variables classified to indicate social status, housing level and standard of living are here discussed together, since on the basis of the present results they cannot be considered to possess any importance as groups. The second best discriminant factor after marital status is *ownership of car*. According to West, in Finnish rural communes, automobile density is growing faster than the economical variables upon which it depends (164). According to the present study too, car ownership appears to be a more dynamic variable than e.g. the mother's or father's social class.

With the combination of variables used in the present study social classification based on the *mother's occupation* seemed to possess, on average, a slightly better discriminant power than that based on the *father's occupation*.

Irrespective of how the socio-economic level was measured, its low level tends to increase the risk of both low birth weight and perinatal mortality. Authors in different parts of the world have arrived at parallel results on this point (10—12, 15, 18, 21, 35, 54, 71, 72, 110, 117, 119, 126, 132, 133, 145, 147, 163, 165, 166). In the present study economic factors increased the risk of perinatal deaths of low birth weight infants. This finding was contradictory to that reported by Ahvenainen and Kunnas in their study of hospital cases the neonatal mortality of low birth weight infants was slightly higher for the higher social class infants (7). When these studies are compared it should be borne in mind that the present series also included prenatal deaths, and that there may be differences between the social classes as regards readiness to seek medical advice for children.

Variables illustrating the *circumstances during childhood* were more important in the analysis concerned with perinatal deaths of infants with birth weights of 2500 g or more than in the other analyses. The most prominent discriminant factor increasing the risk was small *number of mother's siblings*, a finding contradictory to that of the British study, according to which perinatal mortality rate increased in direct proportion to the number of mother's siblings and was visible in all social classes (79). Within the framework of the present study it cannot be said whether size of family as a risk increasing factor should be associated with the relatively high degree of segregation of the population living in the region studied, with the consequence that there might be an increased incidence of conditions due to the meeting up of harmful recessive genes, but this possibility does exist.

Social classification based on the occupation of the child's parents was more important in the present study than that based on the *occupation of the child's maternal grandfather*. The finding is contradictory to that reported

and A 1 concerned with all low birth weight infants than her height, a low weight tending to increase the risk while in the analyses of perinatal deaths height had a *higher* weighting than body weight. Love and Kinch found in their study that *mother's weight* before pregnancy was better correlated with the child's birth weight than maternal height (84) Many authors have found that mothers of lighter weight had children of lower birth weights (9 146 149 150) On the other hand obesity has been found to increase the low birth weight rate (42)

The correlation of maternal weight with perinatal mortality is less obvious In the discriminant function analysis reported by Abernathy et al increasing weight suggested increased perinatal mortality rate (3) while Kaltreider *failed* to trace any correlation between perinatal mortality and maternal weight (75) Sauramo studied abnormally high and low *weights* among Finnish mothers, and found that the foetal mortality rate among the obese was greater (128) Fisher and Frey by contrast, noted no increase in the foetal *mortality* rate among over weight mothers (43)

Menarche age is correlated to the socio-economic environment in that the age of menarche in better socio-economic circumstances is lower (135) on the other hand age of menarche has been found to have correlations, interpreted as genetic, in mother-daughter and sister sister pairs (50) In the present study the age of menarche did not discriminate between the controls and the groups to be separated.

Previous abortions had a moderate weighting in all those discriminant function analyses in which low birth weight infants were the group to be separated The result was parallel to those of earlier studies (20 21 49 138)

Previous low birth weight infants is the variable with the highest or second highest weighting in all discriminant function analyses of low birth weight infants, whereas in that of perinatal deaths with birth weights of 2500 g or more this variable had no appreciable *importance*. Earlier authors have also found this variable to increase the risk of low birth weight and perinatal mortality (20 21 49 88 104 167) In Ounsted's study the risk of bearing a second or further infant of low birth weight was increased when low birth *weight was the* result of intra uterine nutrition but not when it was due to premature delivery (104)

Previous perinatal mortality did not indicate increased risk in any of the present analyses Since previous perinatal mortality is markedly correlated with previous low birth *weight infants*, the distribution of this variable too was different in the high risk and low risk groups of analysis A. In the British perinatal mortality study the correlation of previous perinatal mortality with the present mortality was more pronounced than that of previous low birth weight infants and previous abortions (21)

The number of children under 15 is a variable which covers both parity interval between pregnancies, and number of children who had died before the age of 15 As pointed out before, the question is phrased so that it includes, wherever mothers live in extended family households, children other than the mother's own Component factors are known to exert a parallel effect the expected child's prognosis is made worse by low parity as shown above (p 47) long intervals between pregnancies (163) and deaths of earlier children. It is also possible that the sphere of life associated with extended family households tends to reduce the risk Infant mortality is known to be much more closely connected with socio-economic circumstances than is perinatal mortality (154 158) It is possible that the poor discriminant power of perinatal mortality in the combinations of variables used compared with the variable subsuming the whole childhood mortality rate can be explained against this backround.

In the present study *illegitimacy* was a risk increasing factor in all analyses except that

ment outside the home on either low birth weight rate or perinatal mortality (37 48, 69).

In the analysis of perinatal deaths of small birth weight infants, the mother's *site of work* was of some importance, and it is possible that this is associated with the strenuousness of the work. Ahvenainen and Kunnas came to the conclusion that in birth weight group 1500–2000 grams strenuous work seemed to increase neonatal mortality (7)

In the analysis concerning perinatal deaths of infants with birth weights of 2500 g or more the mother's *posture at work* played some part in that sedentary work tended to increase the risk. This finding, perhaps, may be connected with placental circulation (78, 125).

The level of industrialization in the community was of the greatest importance only in the analyses of perinatal deaths. The regional developmental level in Finland is associated with the degree of industrialization, the less developed regions being predominantly agricultural no industrial slums exist in Finland. The indicators used to measure the degree of industrialization were the income level (taxable income of private persons per capita) the degree of industrialization (the ratio (%) of those engaged in industry to total economically active population) the degree of industrialization (number of wage earners and salaried employees engaged in industry per 1,000 inhabitans) the ratio (%) of those engaged in agriculture and forestry to the total population the financial position of the commune the density of population (resident population per sq. km of land area) the degree of electrification (the ratio (%) of dwellings equipped with electricity to total dwellings) cars per 1,000 inhabitants the ratio (%) of those born in the commune to the total corresponding age groups the ratio (%) of those with a middle-school background to the corresponding age groups the ratio (%) of those engaged in the service industries (in addition to services proper commerce, storage, transport, and communications) to total economically active population the ratio (%) of those living in non-administrative urban settlements to the total population the ratio (%) of the dwellings equipped with water pipes to total dwellings the length of public highways relative to the land area the mean *cultivated area of farms with at least 2* hectares of arable land migration (balance of migration per 1,000 of mean population) home lending by public libraries (books per capita) infant mortality (infant deaths per 1,000 live births) (106).

The *nature of the community* urban/rural also has a high discriminant power in analyses of perinatal deaths. Regional fluctuations in mortality are well known, and comparisons have been made between countries (140, 154 158), between different regions (21 162) and between sectors of one region having different degrees of development (35 166) In the less developed regions mortality rates are usually higher In international comparisons, however infant mortality and perinatal mortality are no longer directly correlated with the national income level. This is particularly noticeable in the United States where infant and perinatal mortality rates today are definitely higher than in many countries of Western Europe (140, 158). The causes of this difference are far from obvious, since mortality rates lower than those of the United States are now recorded even in many countries where the rates in the early decades of the 20th century were considerably higher than in the United States. Research into the differences in perinatal and infant mortality between countries has been able to suggest only two explanations for the lag of the United States, viz. the different distribution of birth weights, the low birth weight rate being higher in the United States, and the contrast in the financing and administration of medical care (158).

The variable *internal migration* separates the groups of perinatal deaths from the control group distinctly *nonmigration* being characteristic for the risk group, whereas

by Drillien in whose study the occupation of the mother s father was better correlated with low birth weight rate than the occupation of the child s father (37)

Although in the present study the part played by the variables concerned with circumstances during childhood did not appear important, it is possible that the biological variables used largely reflected these circumstances, as pointed out by many earlier authors (79 143 144)

The *mother s school attendance* is often considered a measure of the mother s circumstances during childhood and adolescence Low birth weight rate has been found to be higher for infants of mothers with less school attendance (12 70) In the present study mother's school attendance was a discriminant moderately increasing the risk only in the analysis of perinatal deaths of infants with birth weights of 2500 g or more In the parallel analyses of low birth weight infants, in which the number of variables was smaller the variable *intellectual interest in housekeeping and care of health* acquires, however a moderate weighting

The mother s *subjective attitudes* to the desirability of the pregnancy and her views concerning her own frame of mind during pregnancy played no part in the present study either for birth weight or perinatal mortality Gunter found that psychosomatic and neuropsychiatric traits were more frequent in mothers giving birth to low birth weight infants (63) while according to Davids and De Vault anxiety was correlated with perinatal mortality and low birth weight (33) Abernathy et al. came to the conclusion that psychosomatic symptoms in the mother did not affect the infant s birth weight (1)

Owing to the prospective character of the study all the *smokers* who used to smoke daily before the pregnancy started were combined in one group In the analyses concerned with low birth weight infants, smoking increased the risk whereas in the analyses of infants with birth weights of 2500 g or more smoking discriminated rather towards the control group Table 24 reveals that total perinatal mortality rates were identical for smokers and non-smokers, and reviewed by weight classes the mortality rates of smoking mothers infants were lower the increased low birth weight rates equalizing the mortality rates.

Many earlier authors have reported that the birth weights of smokers infants were significantly lower than those of non smokers (1 19 46 65 74 85 104 120 121 151 170, 173) The differences in birth weights between smokers and non smokers infants fluctuated by an average of 120—229 *grams (1 65 74* 173) According to Abernathy et al., however smoking determines only 1 6 per cent of the birth weight variance (1) Smoking has not been found to affect the gestational length (1 85 170)

The results reported from studies of the effect of smoking on perinatal mortality are different. According to the prospective study by Frazier et al smoking did not affect neonatal mortality while smokers had a significantly higher stillbirth rate (46) Underwood et al found that the stillbirth rate among smokers showed no significant increase (151) Jarvinen and Österlund found that smoking did not affect perinatal mortality (74) and Yerushalmy reported in his prospective study that the survival rate of low birth weight infants of smoking mothers was statistically significantly higher than that of non smokers (170) In British studies, on the other hand, smoking definitely increased mortality (19 120)

The *amount of work* performed by the mother did not in the present study increase the risk of low birth weight or perinatal mortality The finding was the same irrespective of whether the mother worked at home or had gainful employment. Stewart assumed that gainful employment together with housekeeping chores increased the low birth weight rate (139) but no other authors report any effect of mother s gainful employ

The variable *distance from population centres* increased the risk in all analyses if it was small, and thus supports the above hypothesis of adverse factors connected with urban life. This variable also brings out such a factor in the analysis of perinatal deaths, in which many variables emphasize the risk increasing aspect of large distances.

Two of the distance standards measure the distance from medical care centres. The distance from an *antenatal clinic* was of no importance in any of the analyses, which suggests that the network of antenatal clinics is sufficiently dense. But the *distance from medical officer* tends to increase the risk in all analyses. Physicians usually live in major centres of population, and therefore this variable, besides measuring the distance of medical care unit, also measures other developmental levels. In a health survey carried out in Finland (114) the number of diseased people was found to increase as distance from the nearest physician grew. The same study revealed that people living at a distance from any physician had incomes below the average and more often lived in communities with fewer medical officers per head of population. The cumulative effect of various adverse factors, typical of underdeveloped regions, also manifests itself in this way (99)

c Total result of the discriminant function analyses

The discriminant function analyses which were carried out did not reveal particularly many new features concerning the individual variables. The study showed that in multivariable analysis the effect of the individual variables remains roughly the same as can be expected from studies by the conventional statistical methods.

However the method of analysis used revealed more distinctly than other methods the fact that mothers of low birth weight infants can be better distinguished from those of controls by means of a battery of variables composed of biological and socio-economic criteria than mothers of infants with birth weights of 2500 g or more that died. It may be assumed that if additional, purely medical variables were used, this difference would either be reduced or the group of infants with birth weights of 2500 g or more could be more readily separated.

Multi variable analysis also reveals the importance of the various factors within the combination of variables used. Perinatal deaths of low birth weight infants were distinguished more emphatically by poverty factors and those of infants with birth weights of 2500 g or more by factors associated with the mother's parents than other groups. The urban way of life seemed to increase the risk in low birth weight infants as a group more than in others.

Multi variable analysis also opens new perspectives for the study of the characteristics of infants assigned to particular risk groups. Combination of the effect of several factors, for example, makes more clearly manifest an abnormal intrauterine growth rate in various groups of mothers. Many other questions concerning the newborn baby may be illuminated in this way when the group studied need not originally be defined on the basis of the child's characteristics. A typical question of this type is the extent to which the factors producing low birth weight also produce an unbalanced conception of female infants. This question is difficult to answer if the groups are separated by birth weight, since girls have lower birth weights. Similarly it may be assumed that additional information can be obtained on other biological or pathophysiological aspects concerning the infant and believed to be associated with intrauterine conditions.

The result of the discriminant function analyses is also of practical significance, especially for babies of low birth weight. The identifiable high risk group covers about 40 per cent of all low birth weight infants although the group is only just under 14 per cent of all the cases. When the total population

in analysis A the risk of low birth weight is increased by internal migration The weighting for the variable in this analysis is however smaller and when this 43 variable analysis is compared with the 27-variable analysis A 1 the weighting in the different combination of variables is further reduced and has a reverse effect.

In Illsley's study internal migration was correlated with a lower low birth weight rate, but the study was mainly concerned with migration from one city to another (70) As can be seen from Table 22 only 8 5 per cent of the present migrants had been urban dwellers before.

Internal migration that is to say change of place of residence, is connected with many other sociological phenomena in the first place occupational mobility It is therefore also associated with vertical social mobility Internal migrants contain various groups, and the motivation for change of place of residence varies from group to group (e.g unemployed domestic help etc versus professions with high educational standards) (70)

Internal migration often has national characteristics In Finland for example, women migrate more frequently than men but this is not a universal feature (153) The predominance of women among migrants has been attributed to the relatively great economic and social independence of women in these communities (95) Some studies of internal migration suggest that the migrants differed favourably in the characteristics measured (school progress, intelligence tests) from the non migrants (70 153) The correlation recorded in the present study between internal migration and low mortality rates may be linked with the biological and social characteristics of the migrants on the basis of which they made better mothers Another pattern of explanation is that, while moving about, these persons acquired more information on family planning, medical care, and other factors tending to reduce mortality

The finding that internal migration is associated with lower mortality while the low birth weight rate is identical to that among the non-migrants and that in a certain combination of variables internal migration is a risk increasing factor is of considerable interest. It may be associated with the constancy of the low birth weight rates in other words, the fact that the tendency to low birth weights is not easy to correct, a recognized and difficult problem (13 29 158)

The identical low birth weight rates among migrants and non migrants do not necessarily mean that the causative factors resulting in low birth weight infants also were identical. The low birth weights of some infants may be attributed to purely medical reasons, and be removable by medical means. In those groups with higher total mortality rates, the groups of non migrants, these reasons may be assumed to be the most important.

According to this hypothesis, there should be other factors contributing towards the low birth weight among internal migrants. In Finland internal migration is largely migration from a rural to an urban environment. Raiha has emphasized in many contexts that low birth weight rates are lower in rural districts, provided conditions are otherwise similar (122—124) A similar finding was made in a study based on extensive statistical information (157) according to which the mean birth weight of infants in the United States was significantly higher in rural than urban areas, while the low birth weight rates were lower The same finding was made when large metropolises were compared with non metropolises and the metropolitan counties with non metropolitan counties the mean birth weights in the latter were higher than in the former (157) In this study the different parity distributions in the regions compared largely accounted for the differences recorded (157) Other factors associated with the urban way of life which increase the low birth weight risk await detailed investigation but the rural way of life may be assumed to be physically healthier

The variable *distance from population centres* increased the risk in all analyses if it was small, and thus supports the above hypothesis of adverse factors connected with urban life. This variable also brings out such a factor in the analysis of perinatal deaths, in which many variables emphasize the risk increasing aspect of large distances.

Two of the distance standards measure the distance from medical care centres. The distance from an *antenatal clinic* was of no importance in any of the analyses, which suggests that the network of antenatal clinics is sufficiently dense. But the *distance from medical officer* tends to increase the risk in all analyses. Physicians usually live in major centres of population, and therefore this variable, besides measuring the distance of medical care unit, also measures other developmental levels. In a health survey carried out in Finland (114) the number of diseased people was found to increase as distance from the nearest physician grew. The same study revealed that people living at a distance from any physician had incomes below the average and more often lived in communities with fewer medical officers per head of population. The cumulative effect of various adverse factors, typical of underdeveloped regions, also manifests itself in this way (99)

c Total result of the discriminant function analyses

The discriminant function analyses which were carried out did not reveal particularly many new features concerning the individual variables. The study showed that in multi variable analysis the effect of the individual variables remains roughly the same as can be expected from studies by the conventional statistical methods.

However the method of analysis used revealed more distinctly than other methods the fact that mothers of low birth weight infants can be better distinguished from those of controls by means of a battery of variables composed of biological and socio-economic criteria than mothers of infants with birth weights of 2500 g or more that died. It may be assumed that if additional, purely medical variables were used, this difference would either be reduced or the group of infants with birth weights of 2500 g or more could be more readily separated.

Multi variable analysis also reveals the importance of the various factors within the combination of variables used. Perinatal deaths of low birth weight infants were distinguished more emphatically by poverty factors and those of infants with birth weights of 2500 g or more by factors associated with the mother's parents than other groups. The urban way of life seemed to increase the risk in low birth weight infants as a group more than in others.

Multi variable analysis also opens new perspectives for the study of the characteristics of infants assigned to particular risk groups. Combination of the effect of several factors, for example, makes more clearly manifest an abnormal intrauterine growth rate in various groups of mothers. Many other questions concerning the newborn baby may be illuminated in this way when the group studied need not originally be defined on the basis of the child's characteristics. A typical question of this type is the extent to which the factors producing low birth weight also produce an unbalanced conception of female infants. This question is difficult to answer if the groups are separated by birth weight, since girls have lower birth weights. Similarly it may be assumed that additional information can be obtained on other biological or pathophysiological aspects concerning the infant and believed to be associated with intrauterine conditions.

The result of the discriminant function analyses is also of practical significance, especially for babies of low birth weight. The identifiable high risk group covers about 40 per cent of all low birth weight infants although the group is only just under 14 per cent of all the cases. When the total population

of mothers is involved advance identification of such a high proportion of low birth weight infants is a remarkable result. The low birth weight rate of 12.5 per cent of the identifiable high risk group differs markedly from the rate for the remaining group which is 2.8 per cent The difference between mortality rates, 51 4 per thousand and 19 3 per thousand, aLo stands out. The mean birth weight of the non low birth weight infants assigned to the high risk group was also lower than in the low risk group Higher mortality rates have been found to be connected with the lower birth weights Survivals may be assumed to represent different levels which can be measured by varying degrees of health for example by mortality rates after the perinatal period e.g during infancy and later childhood Were this assumption accepted the health of the infants of the high risk group with birth weights of 2500 g or more and living at the end of the perinatal period would be poorer and the later mortality rates during childhood higher than those of the infants assigned to the low risk group These cases would represent an above-average level of health in the high risk group yet an increased risk which should be recognized. Detailed investigation of these aspects must, however be postponed to the second continuation section of the present study project.

Discriminant function analysis might be useful in practical health care in antenatal clinics. As can be seen from the study of the parallel analyses (p 34) the number of variables required to achieve a discriminant function of the same order of magnitude is considerably smaller than that used in the present study On the basis of the results, a battery of 20 of the best variables would be adequate for practical purposes The best discriminant variables, moreover are based on simple and practical questions which the mothers can easily answer Classification of one case by computer on the basis of a ready made discriminant function of 20 variables costs mk 1.50 (36 USA cents) This price can be compared with the price of mk 7 0 laboratories charge for blood group determination, or alternatively for an Rh antibody test. As the mothers would manage the completion of the questionnaire largely on their own the mailing and other administrative work to be done by the medical personnel in risk group classification would roughly equal that in blood sampling

An essential difference in this comparison is of course that the information supplied by blood group and Rh antibody tests leads to specific treatment, depending on the information obtained Identification of high risk groups aims at intensified antenatal care and adequate obstetric treatment, although their specificity or potential therapy on many points is not yet comparable e g with the management of blood group immunizations.

On the other hand many of the factors in question i.e. discriminant variables, may be known without the help of a computer This is partly true, but one-third of the series are, for example, primiparas, one-fifth are smokers, and over 8 per cent have previous low birth weight infants — hence the various individual variables make the identifiable risk group so large that adequate care cannot be provided from the medical care resources available

It is essential to continue the analyses by complementing the variables with important medical data obtainable at the beginning of pregnancy such as toxaemia, blood group immunizations and maternal diabetes. By this means it is possible to estimate the total capacity of discriminant function analyses for identification of high risk groups in the earliest phase of pregnancy

Probability classification by discriminant function analysis is particularly useful for practical work in regions with few physicians and long distances, but with a sufficient net work of antenatal clinics and high educational level of the population In a region of this type antenatal clinic work could be very much

intensified for the high risk cases by means of a classification programme derived from the results of the present study

Knowledge of how good results might be obtainable in the prophylaxis of low birth weight infants is far from complete. There is a need for simultaneous research into, and intensive work for early identification of high risk cases at the beginning of pregnancy thorough medical examination of the elicited high risk cases, and intensified obstetric and pediatric care.

Low birth weight rate is also a considerable economic issue. Prophylaxis is much less expensive than the provision of care for low birth weight infants (96) not to mention the fact that not all problems associated with the subject are measurable in terms of money

of mothers is involved advance identification of such a high proportion of low birth weight infants is a remarkable result. The low birth weight rate of 12.5 per cent of the identifiable high risk group differs markedly from the rate for the remaining group which is 2 8 per cent The difference between mortality rates, 51 4 per thousand and 19 3 per thousand, also stands out. The mean birth weight of the non low birth weight infants assigned to the high risk group was also lower than in the low risk group Higher mortality rates have been found to be connected with the lower birth weights. Survivals may be assumed to represent different levels which can be measured by varying degrees of health for example by mortality rates after the perinatal period, e.g during infancy and later childhood. Were this assumption accepted, the health of the infants of the high risk group with birth weights of 2500 g or more and living at the end of the perinatal period would be poorer and the later mortality rates during childhood higher than those of the infants assigned to the low risk group These cases would represent an above-average level of health in the high risk group yet an increased risk which should be recognized Detailed investigation of these aspects must, however be postponed to the second, continuation section of the present study project.

Discriminant function analysis might be useful in practical health care in antenatal clinics. As can be seen from the study of the parallel analyses (p 34) the number of variables required to achieve a discriminant function of the same order of magnitude is considerably smaller than that used in the present study On the basis of the results, a battery of 20 of the best variables would be adequate for practical purposes. The best discriminant variables, moreover are based on simple and practical questions which the mothers can easily answer Classification of one case by computer on the basis of a ready made discriminant function of 20 variables costs mk 1.50 (36 USA cents) This price can be compared with the price of mk 7.0 labora tories charge for blood group determination, or alternatively for an Rh antibody test. As the mothers would manage the completion of the questionnaire largely on their own the mailing and other administrative work to be done by the medical personnel in risk group classification would roughly equal that in blood sampling

An essential difference in this comparison is of course that the information supplied by blood group and Rh antibody tests leads to specific treatment depending on the informa tion obtained. Identification of high risk groups aims at intensified antenatal care and adequate obstetric treatment, although their specificity or potential therapy on many points is not yet comparable e g with the man agement of blood group immunizations

On the other hand, many of the factors in question i e discriminant variables, may be known without the help of a computer This is partly true, but one-third of the series are, for example, primiparas, one-fifth are smokers and over 8 per cent have previous low birth weight infants — hence the various individual variables make the identifiable risk group so large that adequate care cannot be provided from the medical care resources available

It is essential to continue the analyses by complementing the variables with important medical data obtainable at the beginning of pregnancy such as toxaemia blood group immunizations, and maternal diabetes. By this means it is possible to estimate the total capacity of discriminant function analyses for identification of high risk groups in the earliest phase of pregnancy

Probability classification by discriminant function analysis is particularly useful for practical work in regions with few physicians and long distances, but with a sufficient net work of antenatal clinics and high educational level of the population In a region of this type antenatal clinic work could be very much

function separated all infants with birth weight of less than 2500 g as a group.

All the groups used in discriminant function analyses were formed by probability classification based on the discriminant function of each analysis. The total number of cases in the study was classified by the probability classification based on the discriminant function analysis of all infants with birth weights under 2500 g. The characteristics of the mothers and infants of the risk groups identifiable by this method were calculated. With increasing probability of risk, the mean birth weight and mean length at birth decrease, while mortality rate and the rate of infants with birth weight under 2500 g increase sharply. The combined perinatal mortality rate of the high risk groups was 51.4 per thousand and the frequency of birth weight under 2500 g was 12.5 per cent while for the remaining low risk group the figures were 19.3 per thousand and 2.8 per cent, respectively. The high risk group contained 41 per cent of all infants with birth weight under 2500 g and corresponded to roughly 14 per cent of all the cases in the series.

The lower mean birth weight of the infants of high risk groups is distinctly apparent as early as in the 29th to 30th weeks of gestation. The gestational phases according to which various differences in intrauterine growth were demonstrable, and the use of multivariable analyses to trace these differences, were discussed.

In conclusion, the value of probability classification on the basis of the results of discriminant function analysis for early identification of risk group in practical antenatal clinic work was considered.

Summary

The study covered 11 905 (11 931) single births in North Finland during one year (1966) which was approximately 96 per cent of all births in the region during this period

Variations in birth weight and gestational length were presented and intrauterine growth curves by percentile values calculated

The mortality rate calculated per weight group was lowest for the weight range of 3500—3999 grams and in the 40th week of gestation On the intrauterine growth curves, the mortality rate was lowest from the 50th to the 90th percentiles double the lowest rate between the 10th and 50th percentiles, and ten times the lowest rate in the area under the 10th percentile Above the 90th percentile the mortality rate was slightly higher than for the 50—90 percentile range in pre-term but not in full term births. A special study was made of the effect of inclusion or exclusion of macerated stillbirths in a comparison of this type.

The correlations of the maternal biological characteristics and socio-economic circum stances with low birth weight rates and perinatal mortality rates were calculated and the possibility of predicting the latter on the basis of the former was estimated These calculations were carried out by discriminant function analysis. The groups to be separated by analysis were 1000 control cases (birth weight 2500 g or more living at the end of perinatal period and gestational age 38—42 weeks, in cases where it was known) taken by random sampling from among some 10 000 cases, and in the different analyses one each of the following groups (a) birth weight less than 2500 g survivals and deaths, 499 cases, (b) birth weight less than 2500 g deaths, 164 cases, and (c) birth weight 2500 g or more, deaths, 119 cases.

The variables in the discriminant function analysis were maternal characteristics, of which none had anything to do with the course of pregnancy delivery or the infant born. A total of 47 variables were used and as far as they were concerned the study was prospective. According to their contents, the variables belonged to the following groups. biological characteristics social status, condi tions during childhood school attendance and intellectual interest, attitudes, smoking work ing housing level standard of living, internal migration and character of the current and earlier places of residence.

Parallel analyses, with a number of different variables were carried out on the groups with weights less than 2500 g The purpose was to illustrate the effect of a different combination and number of variables.

In all the analyses in which infants weighing less than 2500 g at birth were the group to be separated the discriminant function was statistically highly significant, and in the analysis concerned with perinatal deaths of infants weighing 2500 g or more at birth it was statistically significant.

In all analyses the maternal biological cha racteristics were the essential discriminant factors. Poverty factors were better discrim inants for the perinatal deaths of infants with birth weights under 2500 g than others, while factors associated with the mother s parents discriminated the perinatal deaths of infants with birth weight of 2500 g or more All perinatal deaths were distinguished by region al underdevelopment and lack of internal migration while factors associated with ur

bination separated all infants with birth weight of less than 2500 g as a group.

All the groups used in discriminant function analyses were formed by probability classification based on the discriminant function of each analysis. The total number of cases in the study was classified by the probability classification based on the discriminant function analysis of all infants with birth weights under 2500 g. The characteristics of the mothers and infants of the risk groups identifiable by this method were calculated. With increasing probability of risk, the mean birth weight and mean length at birth decrease, while mortality rate and the rate of infants with birth weight under 2500 g increase sharply. The combined perinatal mortality rate of the high risk groups was 51.4 per thousand and the frequency of birth weight under 2500 g was 12.5 per cent while for the remaining low risk group the figures were 19.3 per thousand and 2.8 per cent, respectively. The high risk group contained 41 per cent of all infants with birth weight under 2500 g and corresponded to roughly 14 per cent of all the cases in the series.

The lower mean birth weight of the infants of high risk groups is distinctly apparent as early as in the 29th to 30th weeks of gestation. The gestational phases according to which various differences in intrauterine growth were demonstrable, and the use of multivariable analyses to trace these differences, were discussed.

In conclusion the value of probability classification on the basis of the results of discriminant function analysis for early identification of risk group in practical antenatal clinic work was considered.

Acknowledgements

In December 1964 my teacher and chief Professor Ole Wasz Höckert, M. D., Head of the Department of Pediatrics at the University of Oulu suggested that I study the correlation between the birth weight of babies and the socio-economic conditions of the mothers. The help of Professor Wasz Hockert enabled me to enlarge the scope of this work beyond that originally envisaged I appreciate very much the unflagging interest which he showed in all stages of this project and his valuable advice.

I have had many helpful discussions on the obstetrical points of this study with Professor Pentti A Järvinen M D., Head of the Department of Gynaecology and Obstetrics of the University of Oulu

Professor Tuomas Peltonen M D Head of the Department of Pediatrics at the University of Turku has shown a keen interest in this work His criticism and encouragement have both been of great value to me.

Docent Elina Haavio-Mannila, Ph D., gave me her stimulating support and valuable advice on the sociological probelms which arose in this study

Mr Pertti Hyyrynen, M Sc suggested methods of analysis for the statistical section of the work His sound advice was most helpful. I also had many enlightening discussions with Mr Timo Partanen M Sc. on the subject of multiple discriminant analysis

The mathematical analyses were carried out in the Computer Centre of the University of Oulu and in the State Computer Centre in Oulu Thanks are due to the Heads of the Centres, Professor Yrjö Kilpi Ph. D., and Mr Pekka Malinen Licentiate of Technology and to their staff for their cooperation.

Dr Aino Yliruokanen M D., and Dr Lauri Allas, M D., Provincial Medical Officers for the Provinces of Lapland and Oulu, both helped me considerably in collecting the material A lot of help in this matter was also provided by Docent Holger Hultin M. D., Head of the Child Welfare Section of the National Medical Board.

Mrs Pirkko Orell helped me kindly in collecting the literature. Mrs Seija Nieminen drew the graphs.

Mrs Hilkka Kontiopää, M A (Helsinki) and Mrs Valerie Jansen, B A (Leeds) translated the manuscript into English.

Professor John A Davis, F R C.P Director of the Department of Child Health in the University of Manchester kindly gave me some final advice on my thesis, while I was a visiting lecturer in his department.

I wish to express my sincere thanks to all those who have contributed to the completion of this study

Financial aid was received from the Finnish Cultural Foundation Funds for North Finland, from the Medical Research Foundation of Finland and from the Medical Research Foundation of Oulu

Manchester January 1969
P R

References

1 Abernathy J. R., Greenberg, B. G., Wells, H. B. and Frazier T M.: Smoking as an independent variable in multiple regression analysis upon birth weight and gestation. *Amer J Public Health, 56* 626 1966.

2. Abernathy J. R., Greenberg, B. G Grizzle, J E. and Donnelly J F Birth weight, gestation, and crown-heel length as response variables in multivariate analysis. *Amer J Public Health, 56* 1281, 1966.

3 Abernathy J R., Greenberg, B. G., Donnelly J F Application of discriminant functions in perinatal death and survival. *Amer J Obstet Gynec, 95* 860, 1966.

4 Abramowicz, M and Kass, E. H. Pathogenesis and prognosis of prematurity *New Eng J M d, 275* 878, 1966 (I).

5 Abramowicz, M. and Kass, E. H. Pathogenesis and prognosis of prematurity *New Eng J Med 275* 938, 1966 (II).

6 Abramowicz, M. and Kass, E. H. Pathogenesis and prognosis of prematurity *New Eng J Med, 275* 1001 1966 (III).

7 Ahvenainen, E. K. and Kurunas, M. Mortality of premature inf ants. *Ann Paediat Fenn, 9* 168, 1963.

8 Ancul, A. O John, G. B Lucas, W E., Little, W A. and Callagan, D A. Prematurity A more precise approach to identification. Obstet Gynec 24 716, 1964

9 Backman, A and Unadrus, C E. Some factors influencing the rate of prematurity *Acta Obstet Gynec Scand, 42* 211 1963

10 Baird, D The influence of social and economic factors on stillbirths and neonatal deaths. *J Obstet Gynaec B t Comm, 52* 339 1945

11 Baird, D Social and economic factors affecting the mother and child. *Amer J Public Health, 42* 516, 1952.

1 Baird, D and Illsley R. Environment and childbearing. *Proc R y Soc Med, 46*:53, 1953.

13 Bartsch, F and Bergman, P Perinatale Mortalität und ihre Geburtsleitung. Gynaecologia, *158* 143 1964

14 Battaglia, F C., F azier T M. and Hellegers, A E. Birth weight, gestational ge, and pregnancy outcome, with special reference to high birth weight—low gestational age infant. *Pediatrics, 37*:417 1966.

15 Bennett, C. G. and Louis, L. S. Demographic factors influencing birth weight. *Hawaii Med J 18*:239 1959

16. Van den Berg, B J and Yerushalmy J The relationship of the rate of intrauterine growth of infants of low birth weight to mortality morbidity and congenital anomalies. *J Pediat, 69*:531 1966.

17 Billewicz, W Z. and Thomson, A. M.: The effect of maternal social class and stature upon the incidence of prematurity Proc Nutr Soc, *16*:5 1957

18. Blegen, S. D The premature child. The incidence, aetiology mortality and the fate of the survivors. *Acta Paediat*, 42; suppl. 88 1953

19 Bonham, D G. Perinatal mortality *Aust New Zeal J Obstet Gynaec 5* 183 1965.

20. Bruns, P D and Cooper W E. Basic factors influencing premature birth. Clin Obstet Gynec 4 341 1961

21 Butler N. R. and Bonham, D G. Perinatal mortality E. & S. Livingstone LTD Edinburgh and London, 1963

22. Butler N Perinatal death. *Clinics in Develop Med, 19*:74 1965

23 Backström-Jarvinen, L.: Heights and weights of Finnish children and young adults. *Ann Paediat Fenn, 10* suppl. 23, 1964.

24. Backstrom, L. and Kauppinen, M. A.: Lapsen sikiökautinen painonkasvu. *Suom. Lääk.*, 23 1553, 1968

25 Cawley R. H., McKeown, T and Record, R. C Parental stature and birth weight. *Amer J Hum Genet, 6* 448, 1954

26. Chipman, S. S., Lilienfeld, A. M., Greenberg, B. G. and Donnelly J F Research methodology and needs in perinatal studies. Charles C. Thomas Publ., Springfield 1966.

27 Clifford, S. H., Reid, D E. and Worcester J Indices of fetal maturity Pregnancy Wastage, ed. Engle, E. T Charles C. Thomas Publ., Springfield 1953

28. Clifford, S. H.: in A Textbook of Obstetrics, ed. by Reid, D E., Philadelphia, Saunders 1962.

29 Clifford, S. H. High-risk pregnancy I. Preven-

Acknowledgements

In December 1964 my teacher and chief Professor Ole Wasz Höckert, M. D Head of the Department of Pediatrics at the University of Oulu suggested that I study the correlation between the birth weight of babies and the socio-economic conditions of the mothers. The help of Professor Wasz Hockert enabled me to enlarge the scope of this work beyond that originally envisaged I appreciate very much the unflagging interest which he showed in all stages of this project and his valuable advice

I have had many helpful discussions on the obstetrical points of this study with Professor Pentti A Jarvinen M D Head of the Department of Gynaecology and Obstetrics of the University of Oulu.

Professor Tuomas Peltonen M D., Head of the Department of Pediatrics at the University of Turku has shown a keen interest in this work. His criticism and encouragement have both been of great value to me

Docent Elina Haavio-Mannila, Ph D., gave me her stimulating support and valuable advice on the sociological probelms which arose in this study

Mr Pertti Hyyrynen M Sc. suggested methods of analysis for the statistical section of the work His sound advice was most helpful. I also had many enlightening discussions with Mr Timo Partanen M Sc on the subject of multiple discriminant analysis.

The mathematical analyses were carried out in the Computer Centre of the University of Oulu and in the State Computer Centre in Oulu. Thanks are due to the Heads of the Centres, Professor Yrjö Kilpi Ph D., and Mr Pekka Malinen Licentiate of Technology and to their staff for their cooperation

Dr Aino Yliruokanen M D and Dr Lauri Allas, M. D Provincial Medical Officers for the Provinces of Lapland and Oulu both helped me considerably in collecting the material A lot of help in this matter was also provided by Docent Holger Hultin M. D Head of the Child Welfare Section of the National Medical Board

Mrs Pirkko Orell helped me kindly in collecting the literature. Mrs Seija Nieminen drew the graphs.

Mrs Hilkka Kontiopaa, M A (Helsinki) and Mrs Valerie Jansen B A (Leeds) translated the manuscript into English

Professor John A Davis, F R C.P Director of the Department of Child Health in the University of Manchester kindly gave me some final advice on my thesis, while I was a visiting lecturer in his department

I wish to express my sincere thanks to all those who have contributed to the completion of this study

Financial aid was received from the Finnish Cultural Foundation Funds for North Finland from the Medical Research Foundation of Finland and from the Medical Research Foundation of Oulu

Manchester January 1969
P R

63. Gunter, L. M.: Psychopathology and stress in the life experience of mothers of premature infants. *Amer J Obstet Gynec, 86*:333 1963

64. Heady J. A., Stevens, C. F. Daly C. and Mor ris, J. N. Social and biological factors in infant mortality IV Independent effects of social class, region, mother's age and her parity *Lancet, I* 499 1955

65. Herriot, A., Billewicz, W. Z. ad Hytten, F. E.: Cigarette smoking in pregnancy *Lancet 1.771* 1962.

66. Holt, K. Age, growth and maturity of the neonate. *Clinics in Develop Med, 19* 100, 1965

67 Hosemann, H. Schwangerschaftsdauer und Neugeborenegewichte. *Arch Gynaec 176* 109 1948.

68. Houghton, J. W and Ross, W F Birth weights and prematurity rates in Southern Rhodesia. *Trans Roy Soc Trop Med Hyg, 47* 62, 1953

69 Illsley R., Billewicz, W. Z. and Thomson, A. M. Prematurity and paid work during pregnancy *Brit J Prev Soc Med, 8* 153 1953

70 Illsley R., Finlayson, A. and Thompson, B. The moti ation and characteristics of internal mig rants *Milbank Mem Fund Quart, 41*.217 1963

71 Jansen, A. A Birthweight, birthlength, prema turity and neonatal mortality in New Guineans. *Trop Geogr Med, 14* 341 1962.

72 Jayant, K. Birth weight and some other factors in relation to infant survival. A study on an Indian sample *Ann Hum Genet 27*.261 1964

73 Jarvinen, P A Paakarinen, P and Kinnunen, O The fullterm, underdeveloped liveborn infant *Neonatal Studies, 6.3 1957*

74 Jarvinen, P and Osterlund, K Effect of smoking during pregnancy on the fetus, placenta and delivery *Ann Paediat Fenn 9* 18, 1963

75 Kaltreider D F Effects of height and weight on pregnancy and the newborn. Charles C. Thomas Publ Springfield 1963

76 Kang, S and Cho, W Sex ratio at birth of the Korean population *Eugen Quart, 6* 187 1959

77 Karn, M N and Penrose, L. S Birth weight and gestation time in relation to maternal ge, parity and infant survival. *Ann Eugen, 16* 147 1951

78 Kauppinen, M. A The correlation of maternal heart volume with the birth weight of the infan and prematurity *Acta* Obstet Gynec *Scand, 46* suppl 6, 1967

79 Kincaid, J Social pathology of foetal and infant loss. *Brit M d J 1* 1057 1965.

80 Koenigsberger M. R. Judgment of fetal age. I Neurologic evaluation. *Pediat Clin N Amer 13* 823, 1966.

81 Karkkainen, K. Erotteluanalyysin moniulotteisuuden tietokoneella. Tampereen Yliopisto, Tietokonekeskus, Tiedonantoja 6 a, 1967

82. Leunald, J Relationship between length of gestation, birth weight and certain other factors. *Bull WHO*, 26.183 1962.

83 Lindell, A.: Prolonged pregnancy *Acta Ob tet Gynec Scand 35* 136, 1956.

84 Love, E. J. and Kinch, R. A. Factors influencing the birth weight in normal pregnancy *Amer J* Obstet Gynec *91*:342, 1965.

85. Lowe, C. R. Effect of mothers' smoking habits on birth weight of their children. *Brit Med J 2.* 673 1959

86. Lubchenco, L. O Hansman, C., Dressler M. and Boyd, E. Intrauterine growth as estimated from li eborn birth-weight data at 24 to 42 weeks of gestation. *Pediatrics, 32* 793 1963.

87 Malan, A. F Evans, A., De V Smit, W B. and De V Heese, H. Intra-uterine growth. A Study of the birthweights f live-born *infants. S Af Med J 28* 698, 1967

88 MacDonald, I S. Familial predisposition to prematurity *Scot Med J 4* 190, 1959

89 McDonald, A. Retarded foetal growth. *Clinic in Develop Med, 19* 14 1965

90. McKeown, T and Gibson, J R.: Observations on *all births (23,970) in Birmingham*, 1947 II. Birth weight. *Brit J Soc Med, 5*:98, 1951

91 McKeown, T and Gibson, J R Observations on all births (23,970) in Birmingham, 1947 IV Premature births *Brit Med J* 2:513 1951

92. McKeown, T and Record, R. C. Influence of pre-natal environment on correlation between birth weight and parental height. *Amer J Hum Genet* 6.457 1954

93. Millis, J. The influence of maternal age and birth order on the outcome of pregnancy in poor Chinese women. *Ann Hum Genet, 22*.362, 1958.

94 Mitchell, R. G. and Farr V The meaning of maturity and the assessment of maturity at birth. *Clinics in Develop M d 19*:83 1965

95. Moore, W E. Industrialization and social *change. Edited by Hoselitz* and *Moore. Unesco* Mouton, 1963

96. Moritz, C. R. Preventable prematurity time-cost study *Obstet Gynec*, 25.585, 1965.

97 Morton, N. E. The inheritance of human birth weight. *Ann Hum Genet, 20* 125 1955

98 Morton, N. E. Empirical risks in consanguineous marriages: birth weight, gestation time, and measurements of infants. *Amer J Hum Genet, 10* 344 1958.

99 Myrdal, G.: Economic theory and underdeveloped regions. University P perbacks, Methuen, London, 1964.

100. Naeye, R. L. and Kelly J. A.: Judgment of fetal

tion of prematurity the Sine Qua Non for reduction in mental retardation and other neurologic disorders. *New Eng J Med 271* 243 1964
30. Colman H. I and Rienzo, J: The small term baby *Obstet Gynec 19* 87 1962.
31 Connor A., Bennett, C. G and Louis, L. S. K.: Birth weight patterns by race in Hawaii. *Hawaii Med J 16*-626, 1957
32. Cooley W W and Lohnes, P R.: Multivariate procedures for the behavioral sciences. John Wiley & Sons, New York 1966
33 Davids, A. and DeVault, S.: Maternal anxiety during pregnancy and childbirth abnormalities. *Psychosom Med 24*-464 1962.
34 Davis, M. E., Potter E. L. and Bruce, W H.: Pertinent factors in the declining perinatal death rate at the Chicago lying in hospital. Pregnancy Wastage, ed. by Engle, E. T Charles C. Thomas Publ., Springfield 1953
35 Donabedian, A., Rosenfeld, L. S. and Southern, E. M: Infant mortality and socioeconomic status in a metropolitan community *Public Health Rep, 80* 1083 1965
36. Donnelly J F Flowers, C. E., Creadick, R. N Wells, H. B Greenberg, B G and Surles, K. B: Maternal fetal and environmental factors in prematurity *Amer J Obstet Gynec 88*-918 1964
37 Drillien, C. M. The social and economic factors affecting the incidence of premature birth Part I Premature births without complications of pregnancy *J Obstet Gynaec Brit Comm 64* 161 1957
38 Engström, L. and Sterky G Standardkurvor för vikt och längd hos nyfödda barn. *Svensk Läkartidn, 63*-4922, 1966.
39 Erhardt, C. L., Joshi, G B., Nelson, F G Kroll, B H. and Weiner L.: Influence of weight and gestation on perinatal and neonatal mortality by ethnic group. *Amer J Public Health 54* 1841 1964
40. Feldstein, M S and Butler N R. Analysis of factors affecting perinatal mortality A multivariate statistical approach. *Brit J Prev Soc Med 19* 128 1965
41 Feldstein, M S. A binary ariable multipl regression method of analysing factors affecting peri natal mortality and other outcomes of pregnancy *J Roy Statist Soc 129* 61 1966.
42 Field, H. and Davis, R. E. The erweight nullipara. *J Amer Coll Obstet Gynec 19*-423 1962.
43 Fisher J J and Frey I Pregnancy and parturition in the obese patient. *Obstet Gynec 11*-92, 1958
44 Fisher R. A The use of multiple measurements in taxonomic problems. *Ann Eugen, 8* 376 1938
45 Fraccaro, M. A contrib tion to the study of birth weight based on an Italian sample *Ann Hum Genet 20* 282, 1956.
46. Frazier T M., Davis, G H., Goldstein, H. and Goldberg, I D Cigarette smoking and prematurity: a prospective study *Amer J Obstet Gynec 81*-988 1961
47 Fuhrmann, W: Genetics of growth and development of the fetus. *Pediat Clin N Amer 12*. 457 1965
48 Furuhjelm, M.: The influence of the mothers' professional work on the prematurity and perinatal mortality of premature infants. *J Obstet Gynaec Brit Comm, 69*-642, 1962.
49 Gardiner E. M and Yerushalmy J: Familial susceptibil ty to stillbirths and neonatal deaths. *Amer J Hyg 30* (Sec. A): 11 1939
50 Garn, S. M. and Rohmann, C. G: Interaction of nutrition and genetics in the timing of growth and development. *Pediat Clin N Amer 13* 353 1966.
51 Ghosh, S. and Beri, S.: Standard of prematurity for North Indian babies. *Indian J Child Health, 11* 210, 1962.
52 Ghosh, S and Daga, S. Comparison of gestational age and weight as standards of prematurity *J Pediat 71* 173 1967
53 Gibson, J R. and McKeown, T Observations on all births (23 970) in Birmingham, 1947 I Duration of gestation. *Brit J Soc Med 4* 221 1950.
54 Gibson J R. and McKeown, T: Observations on all births (23 970) in Birmingham, 1947 V Birth weight related to economic circumstances of parents. *Brit J Soc Med 5* 259 1951
55 Gibson, J R. and McKeown, T: Observations on all births (23,970) in Birmingham, 1947 VI. Birth weight duration of gestation, and survival related to sex. *Brit J Soc Med* 6 152, 1952.
56. Greenberg, B. G. and Wells, H B: Linear discriminant analysis in perinatal mortality *Amer J Public Health 53* 594 1963
57 Gruenwald, P and Minh, H. N Evaluation of body and organ weights in perinatal pathology *Amer J Obstet Gynec 82* 312, 1961
58 Gruenwald P Dawkins, M and Hepner R.: Chronic depri ation f the fetus. *Sinai Hosp J 11* 51 1963
59 Gruenw ld, P Chronic fetal distress and placental insuff ciency *Biol Neonat 5* 215 1963
60 Gruenwald, P Infants of low birth weight among 5000 del veries. *Pediatric 34* 157 1964
61 Gruenwald P The fetus in prolonged pregnancy *Amer J Obstet Gynec 89* 503 1964
62. Gruenwald, P Growth f the human fetus. I Normal growth and ts variation. *Amer J Obstet Gynec 94* 1112, 1966.

135. Simell, G.: Über das Menarchealter in *Finnland. Acta Paediat Scand, suppl. 84* 193..
136. Sinclair J. C. and Sil erman, W A.: Intra uterine growth in acti tissue mass of the human fetus, ith particular reference to the under grown baby *Pediatrics, 38* 48, 1966.
137 Sotner M. and Pomerance, W.: Studies on prematurity II. Influence of fetal maturity on fatality *am. P diatrics, 6* 872, 1950.
138 Stevenson, S. S Garver K. L. and Siegel, E. Premature and full-term infants. *Amer J Dis Child 94* 169 1957
139 Stewart, A. A note on the obstetric effects of work during pregnancy *Brit J Prev Soc Med, 9* 159 1955.
140 Stitt, P G., Hunt, E. P T ylor R. and Goldstein, S. N U.S. anks eleventh in the care f infants. *Mod Hosp 102* 81 1964
141 Taback, M Birth weight and length f gestation with relation to prematurity *J Amer Med Ass, 146* 897 1951
142 Takkunen, R L. Anthropometric studies on Finnish children *Ann Paediat Fenn, 8* suppl 19 1962.
143 Thomson, A M. Human foetal growth. *B J Nut* 13 158, 1951
144 Thomson, A. M. Maternal st ture and reproductiv efficiency *Eugen Rev 51* 157 1959
145. Thomson, A. M. Prematurity socio-economic and nutritional factors *Bibl Paediat 81* 197 1963.
146. Thomson, A. M. and Billewicz, W Z Nutritional status, maternal physique and reproductive efficiency *Proc Nutr Soc 22* 55 1963
147 Timmer M Prosperity and birthweight in J nese infants *Trop Geogr Med 13* 316, 1961
148 Timonen, S Vara, P and Lokki, O Constitution at birth and duration of pregnancy as indicators of the foetomaternal relationship *Ann Chir Gynaec Fenn 52* 329 1963
149 Timonen, S., Uonla, U Kuusisto, P Vara, P and Lokki, O Effec of certai maternal, foetal and geographical factors on the weight and length of he newborn and on the duration of pregnancy *Ann Chi Gynaec Fenn, 55* 196, 1966.
150 Tompkins, W T Wiehl D G and Mitchell, R. McN The underweight patient as an increased obstetric hazard *Amer J Obstet Gynec 69* 114 1955
151 Underwood, P Hester L. L Laffitte, T jr and Gregg, k V The relationship of smoking to the outcome f pregnancy *Amer J Obstet Gynec 91* 270, 1965
152 Usher R McLean, F and Scott, K. E.: Judgment of fetal ge II. Clinical significance of *fetal age* and an objecti method for its assessment. *P diat Clin N Amer 13* 835 1966.
153. V lkonen, T and Kukkonen, A. Factors in rural out-migration. Yearbook of population research in Finland 1965—66, Vammala, 1966.
154 Verhoestraete, L. J and Puffer R. R.: Challenge of fetal loss, prematurity and infant mortality-A world view *J Amer Med Ass, 167* 951 1958.
155 Vital and health statistics. Data from the national ital statistics system. Natality statistics analysis United States 1962. *Nat Cent H alth Stat ser 21 no 1* Washington, 1964
156. V tal and health statistics. Analytical studies. Infant and perinatal mortality in the United States. *Nat Cent H alth Stat ser 3 no. 4* Washington, 1965
157 Vital and health statistics Data from the national tal statistics system. Weight at birth and surv al of the newborn by geographic divisions and urban and rural areas United States, Early 1950. *Nat Cent H alth Stat ser 21 no. 4* Washington, 1965.
158 Vital and health statistics. Analytical studies. International comparison of perinatal and infant mortality the United States and six West European countries. *Nat Cent H al h Stat ser 3 no. 6* Washington, 1967
159 Vital statistics. Official statistics of Finland, Helsinki, 1968
160 Walker J Clinical obstetric features f prematurity and *intra-uterine* growth retardation. *Clinics in Develop Med 19* 36, 1965
161 Warkany J Monroe, B. B. and Sutherland, B. S Intrauterine growth retardation. *Amer J Dis Child, 102*.249 1961
162 Wast-Höckert, O Juurmen, O and Salovaara, H. Social conditions and public health care in North and South Finland according to statistics. *Ann Hyg Med Soc Fenn, 1* 103 1962.
163 Wells, H. B., Greenberg, B G. and Donnelly J F North Carolina fetal and neonatal death study *Amer J Public Health 48* 1583 1958
164 West, L Automobile density in rural Finnish communes. *Fennia 95 no* 2, Helsinki, 1966.
165 Wigglesworth, J S. Foetal growth retardation. *Brit Med Bull, 22* 13 1966.
166. Willie, C. V and Rothney W B. Racial, ethnic, and income factors in the epidemiology of neonatal mortality *Amer Sociol Rev, 27*:522, 1962.
167 Wilson, M. G., Parmelee, A. H., J and Huggins, M. H.: Prenatal history of infants with birth weights of 1,500 grams or less. *J Pediat, 63* 1140, 1963
168. World Health Organization Expert group on

age. III The pathologist's evaluation. *Pediat Clin N Amer 13* 849 1966
101 Neligan, G A.: Age and size of premature infants. *Develop Med Child Neurol, 7* 75 1965.
102. Neligan, G A community study of the relation ship between birth weight and gestational age *Clinics in Develop Med 19* 28 1965
103 Nixon, W C. W : in Perinatal mortality E. & S. Livingstone LTD Edinburgh and London, 1963
104 Ounsted, M. Maternal constraint of foetal growth in man. *Develop Med Child Neurol 7* 479 1965
105 Ounsted, M.: Unconstrained foetal growth in man. A preliminary note. *Develop Med Child Neurol, 8* 3 1966.
106. Palmgren, K.: Regional differences in the degree of development in Finland. P blications of the National Planning Bureau, Series A 15 Helsinki 1964
107 Parmelee, A H. Prematurity and illegitimacy *Amer J Obstet Gynec 81* 81 1961
108 Parmelee, A. H Stern, E., Chervin G and Minkowski, A.: Gestational age and the size of premature infants. *Biol Neonat 6* 309 1964
109 Parviainen, S.: Über das Schicksal der lebend ur Welt gekommenen Frühgeborenen mit beson derer Rücksicht auf die Prognose der Frühgeborenen der Primi und Multiparen. *Acta Obstet Gynec Scand 25* 32, 1945
110 Peller S.: Mortality past and future *Populat on Stud 1* 405 1948
111 Petersen, W F : Man, weather and sun Thomas Publ. Co., Springfield, 1947
112. Public health and medical care 1966. The official statistics of Finland, Helsinki 1968.
113 Public health in Sweden 1965 Official statistics of Sweden, Stockholm 1967
114 Purola, T Kalimo, E., Sievers, K. and Nyman, K : The utilization of the medical services and ts relationship to morb dity health resources and social factors. Publ of Nat Pension Inst of F nland, Ser A 3 1968
115 Rantakallio, P The optimum birth weight *Ann Paediat Fenn 14* 66, 1968
116. Rao, C. R. Advanced statistical method in biometric research. John Wiley & Sons, New York, 1965
117 Rider R. V Taback, M. and Knobloch, H Associations between premature birth and socioeconomic status. *Amer J Public H alth 45* 1022 1955
118 Ross, R. A Some important factors in perinatal mortal ty statistics in a rural state. *Ame J Obst t Gynec 88* 342, 1964
119 Roszkowski, I Janczewska, E. and Troszynski, M : Relative weight def ciency in the newborn. *Biol Neonat 6* 285 1964
120. Russell C. S., Taylor R. and Maddison, R. N.: Some effects of smoking in pregnancy *J Obstet Gynaec Brit Comm 73* 742, 1966.
121 Russell, C. S., Taylor R. and Law C. E.: Smoking in pregnancy maternal flood pressure, pregnancy outcome, baby weight and growth, and other related factors. A prospective study *Brit J Prev Soc Med 22* 119 1968
122 Räihä, C. E. The incidence of premature births. *Ann Med Intern Fenn, 36* 619 1947
123 Räihä, C. E. and Kauppinen, M : An attempt to decrease perinatal mortality and the rate of premature births. *Develop Med Child Neurol, 5* 225 1963
124 Räihä, C. E.: The possibilities of reducing perinatal mortality *Ann P ediat Fenn, 9* 152, 1963.
125 Räiha, C. E.: Prematurity perinatal mortality and maternal heart volume *G y Hosp Rep, 113* 96, 1964
126. Salber E. J and Bradshaw E. S.: Birth weights of South African babies. *Brit J Soc Med 5* 113, 1951
127 Salber E. J and Bradshaw E. S. Birth weights of South African babies. (II) Effect of birth rank on birth weight *Brit J Soc Med 5*.247 1951
128 Sauramo, H O erweight underweight and mostly normal weight obstetric patients th special reference to gestosis. *Acta Obstet Gynec Scand 29* 361 1950
129 Schlesinger E. a d Allaway N C. The combined effect of birth weight and length of gestation on neonatal mortal ty among single premature births. *Pediatrics 15* 698 1955
130. Schutt, W : Foetal factors in intra terine growth retardation. *Clinics n Develop Med 19* 1 1965
131 Shapiro, S. Influence of birth weight, sex, and plural ty on neonatal loss in the United States. *Amer J Public Health 44* 1142, 1954
132. Shapiro S., Weiner L. and Densen P M.: Comparison f prematurity and perinatal morta lity in a general population and in the popula tion of a prepaid group practice, medical care plan *Amer J Public Health 48* 170, 1958.
133 Shapiro, S., Jacobziner H Densen M. and Weiner L : *Further observations on prematurity* and peri atal mortality a general population and in the population f a prepaid group prac ticemedical care plan. *Amer J Publ Health, 50* 1304 1960.
134 Sil erman, W A. and Sinclair J C. Infants of low birth weight. *New Eng J Med 274* 448 1966.

Appendix 1

Variables used in discriminant function analyses

The question concerning the variable in interview form	Range of values for each variable and explanations
	1 Mother' age
Year of birth	The last 2 digits of year of birth. (18—52)
	2. Mother' height
Mother's height (without shoes) cm measured not known	The last 2 digits of height. (40—76)
	3. Mother weight
Mother weight before pregnancy Not known Weight at first antenatal clinic visit month of gestation.	kg — Kilograms. (33—107) Where weight before pregnancy was not known the kg in — weight of the first antenatal clinic visit was used f obtained before the 4th month of gestation.
	4 Menarche age
Mother age at the beginning of first menstrual period years	Age, years. (10—25)
	5 Mother parity
Para	Number of pregnancies excluding abortions and including the present one. (1—16)
	6. Number f abortions
How man abortions?	Number of abortions divided by the sum of pregnancies carried to term plus abortions.
	7 Previous low birth weight infants
Number of infants with birth weights under 2500 g not known	Number divided by variable 5.
	8 Previous perinatal mortality
Have any children died under four weeks of ge? Yes No If yes, how many	Number divided by variable 5.
	9 Mother marital status
Marital status Married 1 Unmarried, widow or divorced 2	Directly from the reply (1—2)
	10 Mother' occupation
Mother occupation	0 = at home, not trained for any occupation. Occupations were classified I—IV according to their social evaluation. Farmer wif was given the value 2 if land under plough equalled minimum 8 hect ares, and 3 if the area was smaller (0—4)

prematurity Final report. *Technical report series no 27* Geneva, W H.O 1950

169 World Health Organization: Public health aspects of low birth weight. *Technical report series no 217* Geneva, W.H.O 1961

170. Yerushalmy J: Mother's cigarette smoking and survival of infant. *Amer J Obstet Gynec 88* 505 1964

171 Yerushalmy J van den Berg, B J Erhardt, C. L. and Jacobziner H.: Birth weight and gestation as indices of immaturity: neonatal mortality and congenital anomalies of the immature. *Amer J Dis Child, 109* 43, 1965.

172. Ylppö, A Das Wachstum der Frühgeborenen von der Geburt bis zum Schulalter *Z Kinderheilk, 24* 111 1919

173 Zabriskie J R.: Effect of cigaret smoking during pregnancy *Obstet Gynec 21* 405 1963

174 Zaizov R. and Laron Z. Body length and weight at birth and one year of age in different communities in Israel. *Acta P ediat Scand, 55* 524 1966.

21 Mother' school attendance

No school or ambulatory school	0	Directly from reply (0—8)
1—4 years of primary school	1	
5—8 years of primary school or unfinished secondary school	2	
½—2 years of vocational school	3	
Over 2 years of ocational school	4	
5 years of secondary school	5	
More than 5 ears of secondary school	6	
Matriculation	7	
Matriculation and more	8	

22. Intellectual interest in housekeeping and are f health

Does the mother learn about housekeeping, children's care or public health facilities from press, radio or television?		Directly from reply (1—5)
Regularly	1	
Fairly often	2	
Sometimes	3	
Seldom	4	
Never	5	

23 Desirability f the pregnancy

The mother finds tha this pregnancy		Directly from reply (1—3)
occurred at propitious time	1	
would have been more desirable later	2	
should not have occurred at all	3	

24 Mother' frame f mind during pregnancy

Has mother frame of mind during this pregnancy been		Directly from reply (1—3)
usual	1	
depressed	2	
ery depressed	3	

25 Mother' attitude toward support by public authorities

Which of the following alternati es does the mother prefer		Directly from reply (1—3)
One should make continuous efforts to improve one own economic standing	1	
One had better be happy with the conditions one h us in	2	
Public authorities should gi people more help than they do today	3	

26 Mother' smoking

Did the mother smoke at least one cigarette or one pipeful day during the 12 months preceding this pregnancy		Directly from reply (0—1)
0 no		
1 yes		

27 Mother attitude to strenuousness f work

Does he mother consider her occupation (= daily work at home nd/or elsewhere)		Directly from reply (1—5)
ery strenuous	1	
strenuous	2	
moderately strenuous	3	
relati ely easy	4	
easy	5	

11 Father's occupation

Father s occupation

Occupations were classified I—IV as for ariable 10. Farmers w th minimum 8 hectares under plough belonged to class 2, others to class 3 (1—4)

12 Is father a farmer?

Information obtained from reply to variable 11 (1—2)
1 no 2 yes

13 M ther s sector of economy

Directly from reply (0—4)

0 No occupation or not working in the occupation
1 Agriculture forestry fishing
2 Commerce
3 Services (to community sector of economy private persons)
4 Industries, building, communications
Not known

14 Father's sector f economy

Directly from reply (0—6)

0 No occupation
1 Agriculture, forestry fishing
2 Industries (incl. electricity gas, water) crafts
3 Building
4 Commerce
5 Communications
6 Services (to commun ty sector of economy private persons)
Not known

15 Mother's vocational standing

Directly from reply (0—4)

0 No occupation, or not worki g in the occupation
1 Employe self-employed
2 Ma ager official
3 Worker
4 Assisting fam ly member
Not known

16. F the s vocational standing

D rectly from reply (1—5

1 Employer self-employed
2 Manager official
3 Worker
4 Assisting family member
5 No occupation
Not known

17 Occupation of mother s father

Occupati n f mother s father (when mother was 15 years old)

The variable obtained ts alues as nder ariable 11 cept that all farmers were combined with value 3 (1—4)

18 Was m the s f ther farmer?

I formation btained from reply to ariable 17 (1—2)
1 no 2 yes

19 Number f mother sibl gs

Number f mother sisters and brothers (l ving and dead)

N mber e cept th t any umber e ceeding 8 is en ered 8 (0—8)

20 Number f mother s dead sibling

How many of mo her sibli gs died before the ge of 15?

Number of dead siblings di ded by total mber of siblings.

21 Mother school attendance

No school or ambulatory school	0	Directly from reply (0—8)
1—4 years of primary school	1	
5—8 years of primary school or unfinished secondary school	2	
½—2 years of vocational school	3	
Over 2 years of vocational school	4	
5 years of secondary school	5	
More than 5 years of secondary school	6	
Matriculation	7	
Matriculation and more	8	

22 Intellectual interest in housekeeping and care of health

Does the mother learn about housekeeping, children's care or public health facilities from press, radio or television?		Directly from reply (1—5)
Regularly	1	
Fairly often	2	
Sometimes	3	
Seldom	4	
Never	5	

23 Desirability of the pregnancy

The mother finds that this pregnancy		Directly from reply (1—3)
occurred at propitious time	1	
would have been more desirable later	2	
should not have occurred at all	3	

24 Mother's frame of mind during pregnancy

Has mother's frame of mind during this pregnancy been		Directly from reply (1—3)
as usual	1	
depressed	2	
very depressed	3	

25 Mother's attitude towards support by public authorities

Which of the following alternatives does the mother prefer		Directly from reply (1—3)
One should make continuous efforts to improve one's own economic standing	1	
One had better be happy with the conditions one lives in	2	
Public authorities should give people more help than they do today	3	

26. Mother's smoking

Did the mother smoke at least one cigarette or one pipeful a day during the 12 months preceding this pregnancy — Directly from reply (0—1)

0 no
1 yes

27 Mother's attitude to strenuousness of work

Does the mother consider her occupation (= daily work at home and/or elsewhere)		Directly from reply (1—5)
very strenuous	1	
strenuous	2	
moderately strenuous	3	
relatively easy	4	
easy	5	

11 Father's occupation

Father s occupation

Occupations were classified I—IV as for variable 10. Farmers w th minimum 8 hectares under plough belonged to class 2, *others to class 3 (1—4)*

12 Is father a farmer?

Information obtained from reply to variable 11 (1—2)
1 no 2 yes

13 Mother's sector of economy

Directly from reply (0—4)

0 No occupation, or not worki g in the occupation
1 Agriculture, forestry fishing
2 Commerce
3 Services (to community sector of economy private persons)
4 I d stries, building, communications
Not known

14 Father s sect of economy

Directly from reply (0—6)

0 No occupation
1 Agriculture, forestry fishing
2 Industries (incl. electricity gas, water), crafts
3 Buildi g
4 Commerce
5 Communications
6 Services (to community sector f economy pri ate persons)
Not known

15 Mother's vocational standing

Di ectly from reply (0—4)

0 No occupation, or not working in the occupation
1 Employer self-employed
2 Manager official
3 Worker
4 Assisting family member
N t k own

16 Father's vocational standing

Directly from reply (1—5)

1 Employer self-employed
2 Manager official
3 Worker
4 Assisting family member
5 No occupation
Not known

17 Occupation of m the fathe

Occupation of mother s father (when mother was 15 years old)

The variabl obtained ts values as under riable 11 except that all farmers were combined, with alue 3 (1—4)

18 Was mother s f ther farmer?

I formation obtained from reply to v riable 17 (1—2)
1 no 2 yes

19 Number f mother s siblings

Number of mother sisters and brothers (living and dead)

Numbe xcept that any number exceeding 8 is en ered as 8 (0—8)

20 Number f mother' d d sibling

How many of mothe s siblings died before the age of 15?

Numbe of dead sibli gs divided by total umber f siblings.

21 Mother's school attendance

No school or ambulatory school	0	Directly from reply (0—8)
1—4 years of primary school	1	
5—8 years of primary school or unfinished secondary school	2	
½—2 years of vocational school	3	
Over 2 years of vocational school	4	
5 years of secondary school	5	
More than 5 years of secondary school	6	
Matriculation	7	
Matriculation and more	8	

22. Intellectual interest in housekeeping and care of health

Does the mother learn about housekeeping, children care or public health facilities from press, radio or television?		Directly from reply (1—5)
Regularly	1	
Fairly often	2	
Sometimes	3	
Seldom	4	
Never	5	

23 Desirability of the pregnancy

The mother finds that this pregnancy		Directly from reply (1—3)
occurred at propitious time	1	
would have been more desirable later	2	
should not have occurred at all	3	

24 Mother's frame of mind during pregnancy

Has mother's frame of mind during the pregnancy been		Directly from reply (1—3)
as usual	1	
depressed	2	
very depressed	3	

25 Mother's attitude towards support by public authorities

Which of the following alternatives does the mother prefer		Directly from reply (1—3)
One should make continuous efforts to improve one's own economic standing	1	
One had better be happy with the conditions one lives in	2	
Public authorities should give people more help than they do today	3	

26 Mother's smoking

Did the mother smoke at least one cigarette or one pipeful a day during the 12 months preceding this pregnancy? — Directly from reply (0—1)

0 no
1 yes

27 Mother's attitude to strenuousness of work

Does the mother consider her occupation (= daily work at home and/or elsewhere)		Directly from reply (1—5)
very strenuous	1	
strenuous	2	
moderately strenuous	3	
relatively easy	4	
easy	5	

28 Mother's gainful employment

Has the mother been gainfully employed outside her home during this p egnancy? — Directly from reply (1—3)

no 1
mainly half time 2
full time 3

29 Mother's post re at work

Does the mother in her present occupation (= daily work at home and/or elsewhere) mainly — Directly from reply (1—3)

sit 1
stand 2
move about 3

30 Does the mother wo k indoors or outdoors?

Does the mother wo k in her occupation — Directly from reply (1—3)

mainly i doors 1
mainly outdoors 2
indoors and outdoors equally 3

31 Help n housekeeping

Has the mother during pregnancy had in house keep g — Directly from reply (1—3)

paid help 1
help by family members 2
no help 3

32 Size of household

How many persons a e there in the household? persons — N mber of persons except that any number exceeding 9 is entered as 9 (1—9)

33 Numbe f persons under 15 years of age

(Precedi g question continued) How many of them are under 15 years of age? persons — Number of children except that any number exceed ng 8 is entered as 8 (0—8)

34 Number of rooms n family dwelling

How many ooms does the household occupy incl ding kitchen (but excl ding kitchenette, recess for beds, bathroom la atory and any sub-let rooms)? rooms — Number of rooms except that any number exceeding 9 is entered as 9 (1—9)

35 Electricity

Is th family dwelling equipped with electricity — Directly from reply (1—2)

1 yes no

36 Running water

I the family dwell ng equipped with running water — Directly from reply (1—2)

1 yes 2 no

37 House ownership

Does th family own a flat or a house — Directly from reply (1—2)

1 yes 2 no

38 TV set

Television set in the family dwell ng — Directly from reply (1—2)

1 yes 2 o

39 Ownership f ar

Does the family own a car — Directly from reply (1—2)

1 yes 2 o

40 *Degree of industrialization of community*

Place of residence

Developmental score calculated from 18 indices (106) (See page 51) (1.7—9.3)

41 *Nature of place of residence*

Family lives in

town	1	Directly from reply (1—3)
large village or other centre of population	2	
remote village	3	

42. *Internal migration*

Has the mother always lived in the same village, or town?
Yes 1 No 2

Directly from reply (1—2)

43 *Nature of earlier place of residence*

(Preceding question continued)
If not, was her place of residence up to the age of 15 mainly

town	1	Directly from reply (0—3)
large village or other centre of population	2	
remote village	3	
No internal migration	0	

44 *Distance from antenatal clinic*

1 less than 300 m	1	Directly from reply (1—9)
2 0.3— 2.9 km	2	
3 3.0— 9.9 km	3	
4 10.0— 16.9 km	4	
5 17.0— 23.9 km	5	
6 24.0— 30.9 km	6	
7 31.0—100.0 km	7	
8 101 —200 km	8	
9 201 km or more	9	
not known		

45 *Distance from neighbour*

Distance from family dwelling to the nearest neighbour (same classification as for Variable 44)

Directly from reply (1—9)

46 *Distance from centres of population*

Distance from family dwelling to nearest large village or similar (same classification as for Variable 44)

Directly from reply (1—9

47 *Distance from medical officer*

Distance from family dwelling to the nearest physician surgery (same classification as for Variable 44)

Directly from reply (1—9)

28 Mother's gainful employment

Has the mother been gainfully employed outside her home during this pregnancy? no 1 mainly half time 2 full time 3	Directly from reply (1—3)

29 Mother's posture at work

Does the mother in her present occupation (= daily work at home and/or elsewhere) mainly sit 1 stand 2 mo e about 3	Directly from reply (1—3)

30 Does the mother work indoors or outdoors?

Does the mother wo k in her occupation mainly indoors 1 mainly outdoors 2 ndoors and outdoors equally 3	Directly from reply (1—3)

31 Help in housekeeping

Has the mother during pregnancy had in house keeping paid help 1 help by fam ly members 2 no help 3	Directly from reply (1—3)

32 Size of household

How many persons are there in the household? persons	Number of persons except that any number exceeding 9 is entered as 9 (1—9)

33 Number f pe sons under 15 years of age

(Preceding question conti ued) How many of them are under 15 years of age? persons	Number of children except that any number exceeding 8 is entered as 8 (0—8)

34 Number of rooms in family dwelling

How many rooms does the household occupy including kitchen (but excludi g kitchenette, recess for beds, bathroom, lav tory and any sub-let rooms)? rooms	Number of rooms except that any number exceeding 9 is entered as 9 (1—9)

35 Electricity

Is the fam ly dwell ng equipped with electricity 1 yes 2 no	Directly from reply (1—2)

36 R nning water

Is the family dwelling equipped with running water *1 yes 2 no*	Directly from reply (1—2)

37 House ownership

Does the fam ly own a flat or house 1 yes 2 no	*Directly from reply (1—2)*

38 TV set

Television set in the family dwelling 1 yes 2 no	Di ectly from reply (1—2)

39 Ownership of car

Does the family own a car 1 yes 2 no	Di ectly from reply (1—2)

Appendix 3

Grams	25	26	27	28	29	30	31	32	33	34		36	37	38	39	40		42	43	44		46	47	48	Unknown	Total	Mortality rate per thousand
Total	8	11		7	13	16	8	11	11	1	19	17	24	13	20	27	18	10	3	1					18	303	23.
Mortality rate per thousand	000	727.3	14	4 5	138	376.9	133 3	200 3	109 3	142 9	94	83 0	44	30 5	1	6	9 9	30.9	21 3	17 4	23.0	8.0		0	43 6	23.7	

TABLE 28 *Distribution of perinatal deaths by birth weight and by gestational age Perinatal mortality rates per thousand by 100 gram weight groups and by gestational weeks calculated from the figures on the total number of cases given in Table 27*

Appendix 2

Grams	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	Unknown	Total
													Weeks													
5400																			1							1
5300																			1							1
5200														10					1							11
5100														10		10		10	2	1						33
5000																	11	10								21
4900																10			3		1					14
4800																	10	11	4							25
4700													1				20	10	10							41
4600													2	10		10	60	30	7							119
4500									1						10		40	60	10	4						123
4400															20	10	50	40	9	2						131
4300										1			4			31	70	80	17	2	1					206
4200											1		6	1	40	50	12	78	18	3						203
4100												4	2		60	131	100	70	21	7	2					377
4000									1	1	3	2	5	11	70	110	140	102	31	7					30	513
3900									1	1		6	9	20	50	170	180	150	38	3	2	3			11	644
3800							1		1		7	1	20	30	80	200	261	110	34	10	5	1			30	791
3700											4	8	13	71	101	281	222	204	34	2	2	3			30	975
3600								2	1	5	3	9	14	30	160	281	260	140	40	8	7	5			40	1005
3500								1	1	3	8	11	17	41	231	331	330	71	32	9	2	1			10	999
3400									1	3	7	16	24	11	140	291	184	141	30	6	3				40	997
3300								1	3	3	6	11	18	80	160	201	291	61	35	4	7	2			10	893
3200									3	3	3	13	32	111	150	270	102	71	29	12	2	1			30	832
3100							2	1	8		7	15	34	71	140	154	111	60	15	3	3	2				626
3000					1				1	5	10	13	32	61	120	181	80	32	17	3	2	1			20	599
2900					1				2	7	9	18	21	71	51	91	92	41	10	5		2			10	431
2800								1	2	1	12	19	28	43	72	60	35	11	8	4		1			41	338
2700							2	1	4	4	11	12	21	20	33	70	40	11	3						11	343
2600								2	3	1	12	7	18		22	29	1	21	4	3	1				31	147
2500				1				1	3	5	8	15	11	33	10	51	1	10	2							151
2400					1		1		3	4	14	11	7	10	5	14	9	7	1	1				1	5	94
2300						2	1		1	1	3	12	8	8	7	13	5		2						4	67
2200		1	1			1			2	4		5	9	7	6	3	1	2	1	1					3	51
2100		1				2		2	6	3	1	5	7	2	5	4	3	1							2	46
2000			1			1		3	5	3	4	2	5	6	9	2	1			1					3	46
1900				1		1	2	1	1	4	2	3	6	2	1		2									24
1800					1		2		2	4	3	2	2		1										2	19
1700						1	5	1	1	2	2	2	1	2	1		1								2	21
1600	1						3	2		1	1	1	1	1											2	13
1500					1	6		3	2		3	3	2	1												21
1400		1			1	5				2	1	1		1												12
1300				1	3	3	3	1	3	1					1											13
1200		1	2	3		1	2		1					1											2	15
1100			2	1			2			1																6
1000		1		1	1	2	1	1	1	1		2		1												12
900	1	2		1	2		2																		1	9
800	1	1					1		1																1	10
700	3	3		1																					3	10
600				1	2																				1	4
Total	6	11	13	13	13	26	30	24	65	77	149	229	380	777	1656	3050	2725	1657	478	1 3	40	22		1	395	11931

TABLE 27 *Distribution of the total number of cases by birth weight and by gestational age*

SUPPLEMENT 192 · 1969

ACTA PÆDIATRICA SCANDINAVICA

SURVEILLANCE OF ACUTE VIRAL RESPIRATORY DISEASES IN CHILDREN

BY LEENA VIHMA

ALMQVIST & WIKSELL · STOCKHOLM · SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge)

131. Mallila, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw. kr. 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw. kr. 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr. 25.— 1962
134. Müller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr. 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet* June 30, 1962. Sw. kr. 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr. 25.— 1962
137. Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr. 25.— 1962
138. Wallgren, Erik Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr. 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress*, Copenhagen, 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wasz-Höckert, Ole and Donner, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr. 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr. 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963*. Sw. kr. 25.— 1963
147. Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultra-violet Irradiation and Vitamin-D Supply. Sw. kr. 20.— 1963
149. Valaes, Tibor, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr. 25.— 1963
150. Mos, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics*. Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study. Sw. kr. 30.— 1964
155. Engström, Ingo, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics*. Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr. 25.— 1964
157. Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type I ([illegible] Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— [illegible]
158. [illegible] nfant. Sw. kr. 25.— 19[illegible]

Paediatric Congress. kr. 25.— 1965

Disease in Sweden. Sw. kr.

161. Peltonen, T. and Hirvonen, L., Experimental Studies and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Pr[illegible] Health and in Haematological Disease during [illegible] kr. 25.— 1966
163. *Newborn Infant Cry*. Edited by John Lind. Sw. kr. 30.—
164. Böttiger, Margareta, Studies on Immunization with [illegible] and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and [illegible] Bronchiectasis. A Review of 187 Cases in Children with [illegible] up Pulmonary Function Studies in 58. Sw. kr. 20.—
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenil[e Rheuma]toid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. [A Mate]rial of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in C[illegible] nal Study. Sw. kr. 25.— 1966
169. Dahl, Mauri, Intracardiac Phonocardiography of the [illegible] in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 19[illegible]
171. Olding, Lars, Bacterial Infection in Cases of Perinatal [illegible] morphological and bacteriological study based on 264 [illegible] Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chorranis*. Sw. kr. 15.
173. Walsh, S. Zoe, The Esophageal Electrocardiogram dur[ing the] First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum [type. A] clinical study before and after operation with special re[ference] to haemodynamic function. Sw. kr. 25.— 1967
175. Hamilton, Fostil, Vectorcardiographic Studies in [In]fants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress*. 1967. Sw. kr. 15.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatrics. [With] Special Regard to Measurement of the Ventricular [illegible] kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation*. by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jürgen, Clinical Studies on the Antibo[dy Re]sponse to *E. Coli* O-Antigens in Infants and C[hildren with] Urinary Tract Infection, Using [the] Passive H[aemagglutination] Technique. Sw. kr. 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance [in the] Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A [illegible] and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of [illegible] Placental Lipid Metabolism and Transport. Sw.
184. Robertson, Bengt, The intrapulmonary arterial pa[ttern in] infancy and in transposition of the great arteries. Sw. kr. 1968
185. Andersen, Else, Skeletal Maturation of Danish School C[hildren] in Relation to Height, Sexual Development, and Social [Condi]tions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: [A Review] of the Literature and Report of Nine Cases. Sw.
187. Karlberg, Petter, *et al.*, The Development of Children in [a Swe]dish Urban Community. A Prospective Longit[udinal Study.] Sw. kr. 30.— 1969
188. Mossberg, Gunnar W., and Mells, Kerstin, Studies in Ol[illegible] Galactose Malabsorption. A Clinical Study of 6 [illegible] Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of C[arbon] Monoxide in Full-Term Newborn Infants. Sw. kr. 20.—
190. Hörnblad, P. Yngve, Experimental Studies on Closure [of the] Ductus Arteriosus Utilizing Whole-Body [illegible] 1969
191. Koivikko, Antti, Cardiovascular Response of the Neonat[e] to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. 1969
192. Vahlquist, Lasse, Surveillance of Acute Viral Respiratory [illegible] in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Groups at Risk in Low Birth We[ight Infants] and Perinatal Mortality. Sw. kr. 30.— 1969
194. Kuronen, Antti, Studies on the Serum Binding of [illegible] in the Newborn Human Infant. Sw. kr. 30.— 1969

Price Swed. kr 30.—

[Pr]inted by [illegible] by Almqvist & Wiksells Boktryckeri AB Uppsala

SURVEILLANCE OF ACUTE VIRAL RESPIRATORY DISEASES IN CHILDREN

SURVEILLANCE OF ACUTE VIRAL RESPIRATORY DISEASES IN CHILDREN

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 192, 1969

Department of Virology and Children's Hospital, University of Turku
Turku, Finland

SURVEILLANCE OF ACUTE VIRAL RESPIRATORY DISEASES IN CHILDREN

by

Leena Vihma

TURKU 1969

CONTENTS

Printed in Finland

KIRJAPAINO POLYTYPOS TURKU 1969

CONTENTS

Introduction

The acute respiratory infections, as the most common illnesses of man, are of interest to clinicians, epidemiologists and microbiologists. Interest in the respiratory illnesses of adult persons is to some extent due to their great importance as causes of absenteeism, which results in economic loss. These illnesses may lead to complications in patients suffering from other chronic disease and may even be fatal in old patients.

Pediatricians and virologists are concerned with the acute respiratory illnesses of children for somewhat other reasons. The severity of these illnesses, especially in young infants, often directly necessitates the existence of adequate hospital wards and the availability of immediate medical aid. Because of the commonness of acute respiratory diseases in children, the problem of secondary infections is considerable.

Research concerning acute respiratory disease has been extensive and study groups have approached the problem of acute respiratory infections in children in different ways. The patients in children's hospitals and out patient clinics in many countries have been carefully studied. The respiratory cases in children have been recorded in several long term family studies, most of these studies have not been directly concerned with respiratory illnesses of children. In well defined groups of children, e.g. in residential nurseries and in children's homes, the acute respiratory infections have been studied both during epidemics and for longer periods. Even children in some general and pediatric practices have been studied for acute respiratory infections, sometimes concurrently with a hospital series. However no simultaneous studies of respiratory infections both in children living in their normal home environment and in children living in institutions have been reported.

In this study the significance of common viral agents in the etiology of acute respiratory infections in children was evaluated by surveying a group of families and a group of children in a residential nursery. The usefulness of a group of institutionalized children as an index of respiratory disease in the children of the whole community was evaluated.

ogic agents in lower respiratory tract disease (7 34) and in febrile cases of upper respiratory infection (19) The croup syndrome is often associated with parainfluenza virus, particularly type 1 infection (1) Chanock and Parrott (17) estimate that 7 to 16 per cent of all respiratory disease in children is associated with parainfluenza virus infections.

The influenza virus types A and B are sometimes of importance during epidemics, reaching attack rates of 25 to 50 per cent, mainly in children over 5 years old (67) Outbreaks of influenza B virus infection have been described in schools (67) The overall importance of this virus group in the etiology of acute respiratory infections in children is less than that of RS and parainfluenza viruses (17)

Adenoviruses may be associated with all forms of respiratory tract infection (62, 72) Opinions vary on the importance of adenoviruses as a cause of respiratory disease. Chanock et al. (17) estimate 8 to 9 per cent of the acute respiratory disease seen in a children's hospital to be due to adenoviruses. Hilleman et al (33) found evidence of adenovirus infection in only 5 per cent of their patients. From data of several studies van der Veen (72) reckoned the importance of adenoviruses to vary from 2.7 to 25 per cent of respiratory illnesses in children the latter percentage was observed in a hospital series during an adenovirus epidemic in Sweden (64) When the adenovirus types recovered from children with respiratory illnesses were investigated by Vargosko et al (71) the majority were found to belong to types 1 — 2, 5 and 7 These types are known to produce febrile upper respiratory tract infections in infants (62)

In Finland, the occurrence of adenovirus infections in children treated at hospital for acute respiratory illnesses were studied by Jansson et al (37) In 14 per cent an association with adenoviruses was observed. Adenovirus epidemics with respiratory symptoms in children due to types 1 and 2 have been reported by Forssell et al. (25) and due to type 7 by Jansson et al. (38)

Rhinoviruses were found to be associated with 4 to 5 per cent of the respiratory illnesses sampled by Chanock et al. (17) and Hilleman (33) About the same proportion of respiratory infections in children were associated with rhinoviruses in the Medical Research Council's collaborative study in Britain (47)

The respiratory illnesses caused by M pneumoniae undergo wide fluctuations in prevalence from year to year (17) In some periods it has been associated with 9 to 10 per cent of the lower respiratory disease in children (17 43) M pneumoniae is considerably more important as a respiratory pathogen in children over 10 years of age than in infants and young children (28)

FAMILY STUDIES

Several long-term family studies have been programmed in the USA and in Britain, mainly in order to collect information on the occurrence of the common cold. These studies have been reviewed by Tyrrell (69)

In the extensive Cleveland study by Dingle et al. (23) virus isolations and serologic tests were performed. During this 10-year study of 86 families, an incidence of 5 to 8 common respiratory illnesses per year was observed in the children. An adenovirus type 3 outbreak was observed in this study population in 1954 and in a serologic study in the same population 4 per cent of the respiratory infections in children could be attributed to the adenovirus infection. Parainfluenza virus type 3 infections were considered to be common among the children. The influenza A2 pandemic of 1957 coincided with the study; the incidence was 73 per cent in the schoolchildren and 30 per cent in the preschool children. In other influenza A and B outbreaks attack rates of 15 to 25 per cent were reported.

THE VIRAL ETIOLOGY OF ACUTE RESPIRATORY DISEASE IN CHILDREN

Influenza virus infections have been known since the 1930s to occur in children during influenza epidemics (67) In 1954 Huebner *et al.* (35) were the first to demonstrate the adenovirus etiology in acute respiratory tract infections of children. From 1956 onwards, the parainfluenza viruses were recovered from children, parainfluenza virus types 1 and 3 by Chanock *et al.* (18) and parainfluenza virus type 2 by Chanock (13) and Beale *et al.* (4) The following year Chanock *et al.* (20) reported the recovery of respiratory syncytial virus (RS) also known as CCA virus of Morris (51) from infants with respiratory illness.

Viruses belonging to a new group were recovered in 1960 and Kendall *et al* (40) reported the isolation of these rhinoviruses from boarding-school boys, Hilleman *et al.* (33) from younger children. Other respiratory tract pathogens were found among the enteroviruses. Coxsackie B type 5 was reported to be associated with acute respiratory illnesses of children by Babb *et al.* (2) and Vargosko *et al.* (70) Philipson *et al.* (52) and Rosen *et al.* (58) recovered viruses of the ECHO group from children with respiratory disease. Reovirus type 1 infection in institutionalized children was reported by Rosen (57) In 1960 Chanock *et al* (15) found serologic evidence in children of respiratory tract infection with the Eaton agent (*Mycoplasma pneumoniae*)

Since the publication of these findings, much attention has been given to investigations of acute respiratory infections in children Summarizing the available information, Chanock (17) Stuart Harris (67) and Tyrrell (69) have presented estimates of the importance of a number of viruses in acute respiratory diseases of infancy and childhood.

Each of the pathogenic viruses of the respiratory tract can provoke illnesses ranging from inapparent to severe infections, but obviously some of these viruses are more often responsible than other for severe lower respiratory tract involvement (17 67 69)

The RS virus is considered to be the most important viral pathogen in infants. RS infection was detected in 26 to 30 per cent of bronchiolitic illnesses by Chanock *et al.* (17) RS infections occur in epidemics resulting in high infection rates in closed child communities (67 69) In the series of Chanock *et al.* (17) RS virus was associated with 9 5 per cent of all pediatric respiratory illnesses studied. Hilleman *et al.* (33) estimated the importance of RS virus in the outpatient and hospital series at 17—25 per cent of the respiratory infections of children

In Scandinavia Hornsleth (34) has found RS virus to be the etiologic agent in 10 per cent of children with pneumonia. Berglund (7) has reported the same features of RS infection in Finland The epidemiology of the RS virus was followed by Berglund for 3 years, and 4 outbreaks were observed during this period. The agent was found to spread potently among day nursery children and within families. In addition RS virus was recovered from the middle ear exudates of 16 children suffering from RS virus infection

Parainfluenza viruses are important eti

...logic agents in lower respiratory tract disease (17, 34) and in febrile cases of upper respiratory infection (19). The croup syndrome is often associated with parainfluenza virus, particularly type 1, infection (17). Chanock and Parrott (17) estimate that 7 to 16 per cent of all respiratory disease in children is associated with parainfluenza virus infections.

The influenza virus types A and B are sometimes of importance during epidemics, reaching attack rates of 25 to ..0 per cent, mainly in children over 5 years old (67). Outbreaks of influenza B virus infection have been described in schools (67). The overall importance of this virus group in the etiology of acute respiratory infections in children is less than that of RS and parainfluenza viruses (17).

Adenoviruses may be associated with all forms of respiratory tract infection (62, 7?). Opinions vary on the importance of adenoviruses as a cause of respiratory disease. Chanock et al. (17) estimate 8 to 9 per cent of the acute respiratory disease seen in a children's hospital to be due to adenoviruses. Hilleman et al. (33) found evidence of adenovirus infection in only 5 per cent of their patients. From data of several studies van der Veen (7?) reckoned the importance of adenoviruses to vary from ..7 to .. per cent of respiratory illnesses in children, the latter percentage was observed in a hospital series during an adenovirus epidemic in Sweden (64). When the adenovirus types recovered from children with respiratory illnesses were investigated by Vargosko et al. (71), the majority were found to belong to types 1 ..., 3, 5 and 7. These types are known to produce febrile upper respiratory tract infections in infants (62).

In Finland, the occurrence of adenovirus infections in children treated at hospital for acute respiratory illnesses were studied by Jansson et al. (37). In 14 per cent an association with adenoviruses was observed. Adenovirus epidemics with respiratory symptoms in children due to types 1 and 3 have been reported by Forssell et al. (25) and due to type 7 by Jansson et al. (38).

Rhinoviruses were found to be associated with 4 to 6 per cent of the respiratory illnesses sampled by Chanock et al. (17) and Hilleman (33). About the same proportion of respiratory infections in children were associated with rhinoviruses in the Medical Research Council's collaborative study in Britain (47).

The respiratory illnesses caused by *M. pneumoniae* undergo wide fluctuations in prevalence from year to year (17). In some periods it has been associated with 0 to 10 per cent of the lower respiratory disease in children (17, 48). *M. pneumoniae* is considerably more important as a respiratory pathogen in children over 10 years of age than in infants and young children (28).

FAMILY STUDIES

Several long-term family studies have been programmed in the USA and in Britain, mainly in order to collect information on the occurrence of the common cold. These studies have been reviewed by Tyrrell (69).

In the extensive Cleveland study by Dingle et al. (23), virus isolations and serologic tests were performed. During this 10-year study of 86 families, an incidence of 5 to 8 common respiratory illnesses per year was observed in the children. An adenovirus type 3 outbreak was observed in this study population in 1954 and in a serologic study in the same population 4 per cent of the respiratory infections in children could be attributed to the adenovirus infection. Parainfluenza virus type 3 infections were considered to be common among the children. The influenza A2 pandemic of 1957 coincided with the study: the incidence was 73 per cent in the school children and 30 per cent in the preschool children. In other influenza A and B outbreaks attack rates of 15 to .. per cent were reported.

The Virus Watch program of Fox *et al* (26 63 24) was a continuing surveillance of a group of families, living in metropolitan New York for viral infections. The families were residing in two different areas. Respiratory illness rates were lower than in the Cleveland study The respiratory illnesses were associated with adenoviruses in 3 to 4 per cent and with enteroviruses in 4 to 5 per cent in the first period of study and in only 1 per cent in the second period In the latter period rhinoviruses were included in the study and the frequency of respiratory illnesses of children associated with rhinoviruses ranged from 8 to 11 per cent in different age groups.

STUDIES IN GROUPS OF INSTITUTIONALIZED CHILDREN

Bell *et al* (5) carried out the first long term clinical and virologic study of nursery children in Washington, D C The respiratory illnesses were investigated in this large Junior Village study over a period of 3 years. On average, 50 young children were under observation The mean weekly total illness rate was 21.5 per cent. Infections with adenovirus types 1 3 and 5 influenza A2 parainfluenza types 1 and 3 and Coxsackie B type 3 were significantly associated with acute febrile illness. Kapikian *et al* (39) described an RS virus outbreak in Junior Village Eight outbreaks of parainfluenza virus infections were observed (19)

In a residential nursery for children aged less than 5 years with a mean population of 18, observed by Sutton (68) an average of 8 respiratory illnesses occurred per person year During the study period of 8 months, outbreaks of influenza A and parainfluenza type 3 were diagnosed. Fifteen children yielded adenoviruses types 1 2 and 5 but these isolations were not significantly related to respiratory illnesses.

In France Couvreur *et al* (21) report a longitudinal survey of the respira illnesses in a group of infants 4 months to years of age under treatment for tubercul During the 3 years of observation, one epid mic of respiratory disease due to ECHO viru type 7 and one epidemic due to RS viru were detected

A study of acute respiratory disease in children's home in Kansas City was perfor med by Loland *et al* (53) Sixty-one children 2 to 12 years old had an average of 7 il nesses per person year of observation. Tw well defined outbreaks of illness were ass ciated with influenza virus type B and ECHO virus type 20 A parainfluenza virus type outbreak was observed in the children's hom during the fifth year of surveillance in th home (32)

Aitken *et al* (1) observed children unde 3½ years of age in a nursery in Edinburgh f evidence of respiratory illness. During the months of the survey 2 6 respiratory illness were experienced per child Forty two per cen of 105 illnesses were associated with viru infections. RS and adenovirus infections wer observed in 16 cases, parainfluenza type 3 in 15 cases and influenza C infections in 1 cases during the survey Adenovirus infec tions were distributed evenly throughout th study period The other infections occurred in well-defined outbreaks, the influenza outbreak occurring twice

In Finland, Berglund *et al* (8) follow the respiratory infections in a small nurser for 21 months. Two RS virus outbreaks c cided with epidemics involving the whol city There was evidence that one outbrea probably was associated with influenza virus, prevalent in the area at the same time On the average each child had a new attack of respiratory illness every 11 weeks and the infants had respiratory symptoms during 23 per cent of the time they were under observation

Mascoli *et al.* (46) investigated 741 throat

specimens taken from respiratory illness cases in nurseries for detection of rhinoviruses and 3.5 per cent of these specimens yielded rhinoviruses in children aged 3 to 5 years.

Numerous reports dealing with isolated *outbreaks of acute respiratory illnesses asso*ciated with RS virus (41 50 59 66) adenoviruses (73) and enteroviruses (6, 11) in nurseries and other child communities have been published.

Sterner *et al.* (66) reported an outbreak of *M pneumoniae* infection in a home for children. In their surveillance of acute respiratory disease at the children's home in Kansas City Glezen *et al.* (27) included *reports on the mycoplasma. One slowly pro*gressing outbreak of *M pneumoniae* was observed, 27 out of 46 children showing evidence of infection.

The Virus Watch program of Fox *et al* (26 63 24) was a continuing surveillance of a group of families, living in metropolitan New York, for viral infections. The families were residing in two different areas. Respiratory illness rates were lower than in the Cleveland study. The respiratory illnesses were associated with adenoviruses in 3 to 4 per cent and with enteroviruses in 4 to 5 per cent in the first period of study and in only 1 per cent in the second period. In the latter period rhinoviruses were included in the study and the frequency of respiratory illnesses of children associated with rhinoviruses ranged from 8 to 11 per cent in different age groups.

STUDIES IN GROUPS OF INSTITUTIONALIZED CHILDREN

Bell *et al* (5) carried out the first long term clinical and virologic study of nursery children in Washington D C. The respiratory illnesses were investigated in this large Junior Village study over a period of 3 years. On average, 50 young children were under observation. The mean weekly total illness rate was 21 5 per cent. Infections with adenovirus types 1 3 and 5 influenza A2 parainfluenza types 1 and 3 and Coxsackie B type 3 were significantly associated with acute febrile illness. Kapikian *et al* (39) described an RS virus outbreak in Junior Village. Eight outbreaks of parainfluenza virus infections were observed (19).

In a residential nursery for children aged less than 5 years with a mean population of 18 observed by Sutton (68) an average of 8 respiratory illnesses occurred per person year. During the study period of 8 months, outbreaks of influenza A and parainfluenza type 3 were diagnosed. Fifteen children yielded adenoviruses types 1 2 and 5 but these isolations were not significantly related to respiratory illnesses.

In France Couvreur *et al* (21) report a longitudinal survey of the respira illnesses in a group of infants 4 months to years of age under treatment for tuberculos. During the 3 years of observation one epid mic of respiratory disease due to ECHO viru type 7 and one epidemic due to RS v were detected.

A study of acute respiratory diseases in a children's home in Kansas City was perfor med by Poland *et al* (53). Sixty-one childre 2 to 12 years old had an average of 2.7 illnesses per person year of observation. Two well defined outbreaks of illness were associated with influenza virus type B and ECHO virus type 25. A parainfluenza virus type outbreak was observed in the children's home during the fifth year of surveillance in the home (32).

Aitken *et al* (1) observed children under 3½ years of age in a nursery in Edinburgh for evidence of respiratory illness. During the 6 months of the survey 2.6 respiratory illnesses were experienced per child. Forty two per cent of 105 illnesses were associated with virus infections. RS and adenovirus infections were observed in 16 cases, parainfluenza type 3 in 15 cases and influenza C infections in 18 cases during the survey. Adenovirus infections were distributed evenly throughout the study period. The other infections occurred in well-defined outbreaks, the influenza C outbreak occurring twice.

In Finland Berglund *et al* (8) followed the respiratory infections in a small nursery for 21 months. Two RS virus outbreaks coincided with epidemics involving the whole city. There was evidence that one outbreak probably was associated with influenza A2 virus, prevalent in the area at the same time. On the average each child had a new attack of respiratory illness every 11 weeks and the infants had respiratory symptoms during 23 per cent of the time they were under observation.

Mascoli *et al* (46) investigated 741 throat

specimens taken from respiratory illness cases in nurseries for detection of rhinoviruses and 3.5 per cent of these specimens yielded rhinoviruses in children aged 3 to 5 years.

Numerous reports dealing with isolated outbreaks of acute respiratory illnesses associated with RS virus (41 50 59 66) adenoviruses (73) and enteroviruses (6, 11) in nurseries and other child communities have been published.

Sterner *et al.* (66) reported an outbreak of *M. pneumoniae* infection in a home for children. In their surveillance of acute respiratory disease at the children's home in Kansas City Glezen *et al.* (27) included reports on the mycoplasma. One slowly progressing outbreak of *M. pneumoniae* was observed, 27 out of 46 children showing evidence of infection.

The Virus Watch program of Fox *et al* (26 63 24) was a continuing surveillance of a group of families, living in metropolitan New York for viral infections. The families were residing in two different areas. Respiratory illness rates were lower than in the Cleveland study The respiratory illnesses were associated with adenoviruses in 3 to 4 per cent and with enteroviruses in 4 to 5 per cent in the first period of study and in only 1 per cent in the second period. In the latter period rhinoviruses were included in the study and the frequency of respiratory illnesses of children associated with rhinoviruses ranged from 8 to 11 per cent in different age groups.

STUDIES IN GROUPS OF INSTITUTIONALIZED CHILDREN

Bell *et al.* (6) carried out the first long term clinical and virologic study of nursery children in Washington D C The respiratory illnesses were investigated in this large Junior Village study over a period of 3 years. On average 60 young children were under observation. The mean weekly total illness rate was 21.5 per cent. Infections with adenovirus types 1 3 and 5 influenza A2 parainfluenza types 1 and 3 and Coxsackie B type 3 were significantly associated with acute febrile illness. Kapikian *et al* (39) described an RS virus outbreak in Junior Village Eight outbreaks of parainfluenza virus infections were observed (19)

In a residential nursery for children aged less than 6 years with a mean population of 18 observed by Sutton (68) an average of 8 respiratory illnesses occurred per person year During the study period of 8 months, outbreaks of influenza A and parainfluenza type 3 were diagnosed Fifteen children yielded adenoviruses types 1 2 and 5 but these isolations were not significantly related to respiratory illnesses.

In France Couvreur *et al* (21) reported a longitudinal survey of the respiratory illnesses in a group of infants 4 months to 3 years of age under treatment for tuberculosis. During the 3 years of observation one epidemic of respiratory disease due to ECHO virus type 7 and one epidemic due to RS virus were detected.

A study of acute respiratory diseases in a children's home in Kansas City was performed by Holand *et al* (53) Sixty-one children 2 to 12 years old had an average of 2 7 illnesses per person year of observation. Two well defined outbreaks of illness were associated with influenza virus type B and ECHO virus type 20 A parainfluenza virus type 2 outbreak was observed in the children's home during the fifth year of surveillance in this home (32)

Aitken *et al* (1) observed children under 3½ years of age in a nursery in Edinburgh for evidence of respiratory illness. During the 6 months of the survey 2 6 respiratory illnesses were experienced per child Forty two per cent of 105 illnesses were associated with virus infections. RS and adenovirus infections were observed in 10 cases, parainfluenza type 3 in 15 cases and influenza C infections in 18 cases during the survey Adenovirus infections were distributed evenly throughout the study period The other infections occurred in well-defined outbreaks, the influenza C outbreak occurring twice

In Finland Berglund *et al* (8) followed the respiratory infections in a small nursery for 21 months. Two RS virus outbreaks coincided with epidemics involving the whole city There was evidence that one outbreak probably was associated with influenza A2 virus, prevalent in the area at the same time. On the average, each child had a new attack of respiratory illness every 11 weeks and the infants had respiratory symptoms during 23 per cent of the time they were under observation

Mascoli *et al.* (46) investigated 741 throat

Materials and Methods

STUDY POPULATION

Nursery group

The nursery group consisted on infants in a small private residential nursery in Turku, Finland. In this nursery Berglund *et al.* (8) previously performed a study and described the details of the organization and conditions in the nursery. A school for nurses is situated in the neighborhood and the nursery serves as a training place for the student nurses. The hygienic standards in the nursery are high.

The residential nursery is intended for infants under 2 years old. It has 16 beds, 4 small isolation rooms, 4 large rooms for 4 infants each and one big playroom for the older infants. Usually only healthy infants are admitted, but sometimes infants with congenital malformations are taken into the nursery for social reasons. Many of the infants admitted are brought directly from maternity hospitals and stay until an adoption is organized, on average for 4 months. A small number of the infants are at the nursery owing to the temporary or permanent inability of their families to take care of them. Every newcomer is first placed in an isolation room for one week and if no signs of infection are observed the infant is moved to a large room.

During the present surveillance 57 infants, 23 girls and 34 boys, were resident at the nursery. The mean number of infants was 15.0, the mean weekly number the same and the median 15. Table 1 shows the mean monthly numbers of infants in the study.

When space is available, the nursery serves as a "hotel" for infants. The "hotel infants" stay in the isolation rooms; occasionally the older "hotel infants" are allowed to play in the common playroom if they stay for a long time. During the observation period, 87 "hotel infants" visited the nursery. Three stayed for a long time; the mean duration of stay for the remaining 84 infants was 6 days. These "hotel infants" were not included in the study.

Family group

Selection of families. The goal was to find families with at least three children, the youngest of whom was an infant. These infants were to form a comparison group for the nursery infants. They should all be nursed in their homes. Suitable families were picked from the indexes kept in the children's welfare centers. The health sisters made the first inquiries and if the mother appeared willing, the author made a home visit to explain the purpose of the study and the study procedures. The importance of two bleedings in each respiratory illness was stressed. The families were offered free medical consultation and if necessary free laboratory investigations in the Children's Hospital, University of Turku, during the study period.

The first group of families was recruited in September 1965. It consisted of 31 families. Some families were lost and after 6 months of study it was felt, that more families could be observed. In April 1966 a further group of 17 families was included.

Outlines of the Present Study

The significance of viruses as etiologic agents in acute respiratory infections of children was studied. The techniques available adapted to the recovery of four common viral agents, RS, parainfluenza, influenza and adenoviruses, restricted the study mainly to the importance of these viruses.

Another purpose of the study was to evaluate a group institutionalized children as an index of the respiratory illnesses among the children of the whole community.

The objectives were approached by a long term surveillance of acute respiratory illnesses simultaneously in a group of infants in a residential nursery and in a group of families with infants. During the study the occurrence of respiratory illnesses was recorded for epidemiologic purposes. Patients with respiratory symptoms were studied by virus isolation techniques and serologic tests to determine the virus etiology of the acute respiratory illness. For further evalution of the importance of RS, parainfluenza, influenza and adenovirus infections in children, the patients were examined and the clinical data reviewed.

Materials and Methods

STUDY POPULATION

Nursery group

The nursery group consisted on infants in a small private residential nursery in Turku, Finland. In this nursery Berglund *et al.* (8) previously performed a study and described the details of the organization and conditions in the nursery. A school for nurses is situated in the neighborhood and the nursery serves as a training place for the student nurses. The hygienic standards in the nursery are high.

The residential nursery is intended for infants under [illegible] years old. It has 16 beds, [illegible] small isolation rooms, 4 large rooms for 4 infants each and one big playroom for the older infants. Usually only healthy infants are admitted, but sometimes infants with congenital malformations are taken into the nursery for social reasons. Many of the infants admitted are brought directly from maternity hospitals and stay until an adoption is organized, on average for 4 months. A small number of the infants are at the nursery owing to the temporary or permanent inability of their families to take care of them. Every newcomer is first placed in an isolation room for one week and if no signs of infection are observed the infant is moved to a large room.

During the present surveillance 7 infants, 23 girls and 24 boys, were resident at the nursery. The mean number of infants was 15.0; the mean weekly number the same and the median 15. Table 1 shows the mean monthy numbers of infants in the study.

When space is available the nursery serves as a "hotel" for infants. The "hotel infants" stay in the isolation rooms; occasionally the older "hotel infants" are allowed to play in the common playroom if they stay for a long time. During the observation period, 87 "hotel infants" visited the nursery. Three stayed for a long time; the mean duration of stay for the remaining 84 infants was 6 days. These "hotel infants" were not included in the study.

Family group

Selection of families. The goal was to find families with at least three children, the youngest of whom was an infant. These infants were to form a comparison group for the nursery infants. They should all be nursed in their homes. Suitable families were picked from the indexes kept in the children's welfare centers. The health sisters made the first inquiries and if the mother appeared willing, the author made a home visit to explain the purpose of the study and the study procedures. The importance of [illegible] bleedings in each respiratory illness was stressed. The families were offered free medical consultation and if necessary [illegible] laboratory investigations in the Children's Hospital, University of Turku, during the study period.

The first group of families was recruited in September [illegible]. It consisted of [illegible] families. Some families were lost and after [illegible] months of study it was felt that more families should be observed. In April 1968 a further group of [illegible] families was recruited.

Table 1 *Mean number of participants in the study by month*

	Nursery group	Family group				
	Infant	Infants	Children —6 yrs	School children 7—10 yrs	Children 11— yrs	Parents
1965 Sept	15	35	29	35	10	63
Oct.	15	33	29	35	10	62
Nov	16	34	28	35	10	60
Dec.	16	33	28	35	10	60
1966 Jan	17	33	7	34	8	59
Feb.	16	33	7	34	7	58
Mar	14	37	31	38	9	63
Apr	1	34	45	54	16	[illegible]
May	15	3	44	54	16	90
June	14	41	31	4	13	80
July	15	36	[illegible]	34	10	7
Aug	13	43	31	[illegible]	13	80
Sept.	14	49	40	[illegible]	14	80
Oct	15	48	40	49	1	83
Nov	15	47	39	49	1	[illegible]
Dec.	17	4	39	49	11	82
1967 Jan.	16	45	38	47	10	8
Feb.	14	43	3	43	10	76
Mar	13	43	37	45	10	6
Apr	13	43	3	45	10	76
May	14	43	37	44	10	77
June	14	33	[illegible]	28		65
July	14	[illegible]	10	[illegible]	3	60
Aug	16	33	[illegible]	30	0	67
mean	15	40	33	40	19	73

Family population Altogether 48 families were enrolled, with a total of 277 persons (96 parents, 97 female children and 84 male children)

The children were divided into age groups according to the following principles

— Infants. All children under 2 years of age at enrolment in September 1965 or April 1966 The total number of infants was 60 33 girls and 27 boys. The mean number of infants in the study was 40 3 the weekly mean the same and the median number was 41 infants.

— Children 2—6 years of age All children 2 years of age or older at enrolment but not in elementary school during the study period were included in this group The total number of children in this group was 47 20 girls and 27 boys. The mean number of children 2—6 years of age in the study was 30 0 the weekly mean the same and the median 32.

— School-children 7—10 years of age. All children in elementary schools during the study period up to 10 years old were included in this group There were 55 children, 31 girls and 24 boys. The mean number of school-children aged 7—10 years in the study was 40 6 the same as the weekly mean the median was 41

— Children 11 years old and older All the children aged 11 years or more at enrolment were in this group There were only 19 such children The mean number of older children in the study was 10 5 the weekly mean the same and the median 10 children.

The mean number of parents in the study was 72 7 the mean weekly number 72.9 and the median 76

The mean monthly numbers of persons un observation in each of these age groups e shown in Table 1

There is a decline in the mean monthly umber of participants during the summer onths due to loss of children and families om observation during their vacations. leven families dropped out of the study 4 milies because they moved out of town after articipation for on average one year three wo of them in the beginning of the study e after 9 months) because of the laborious udy procedures. Three families did not want o cooperate because f the bleedings and were eleased after being in the study for 4 9 and 1 months. One infant entered a day-nursery nd the family was released after 16 months articipation in the study Two persons in he oldest child group were released one was ent to a tuberculosis sanatorium, the other ft home to study elsewhere.

Description of the population

Ag The mean and the median age of each study group was calculated at the beginning, m ldle and end f the study The results are shown in Table – In the nursery group the standard deviations of the mean ages were 5½ 8½ and 7½ months, respectively On these occasions the youngest infants were 2 months of age, and at the end of the study the oldest infant was – years 7 months old.

In the family infants the standard devia tions of the mean ages were 5½ 7½ and 9½ months, respectively In the families 5 infants were born during the study and at the end the oldest child in the infant group was 3½ years of age.

In the group of children aged 2—6 years, the age range was from – to 6 years, from to 7 years and from 4 to 7 years on the 3 occasions of age estimation.

The ages of the school-children ranged from 5 to 10 from 6 to 11 and from 7 to 1? years in the respective times.

In the group of children 11 years of age or older the oldest were 18 years at the beginning of the study 1 year later one was 19 years old, but at the end of the study the ages ranged from 1 to 17

The youngest mother was — years old and the oldest 45 years when they entered the study and the youngest father was –5 and the oldest 53 years of age.

Social grouping of the families. Most of the families belonged to the middle socioeconomic class (6–) 3 families were of the upper class (5.8 per cent) and 13 from the

Table – *M an and media ages f the study groups*

Study group	Age					
	September 1 1965		September 1, 1966		August 31, 1967	
	Mean	Median	Mean	Median	Mean	Median
Nursery group						
Infant	9½ mo	8 mo	11 mo	3 mo	7½ mo	8 mo
Family group						
inf nts	9 mo	8 mo	1 yr 4½ mo	1 yr 3 mo	2 yrs 4 mo	yrs 3 mo
children —6 yrs	3½ yrs	3 yrs	3 rs	4 yrs	5 yrs	3 yrs
school-children 7—10 yrs	8 yrs	8 yrs	8½ yrs	8 yrs	9½ yrs	9 yrs
childr 11— yrs	14 yrs	14 yrs	15 yrs	13 y	14 yrs	14 yrs
mothers	32 yrs	31 yrs	32 yrs	32 yrs	33 yrs	33 yrs
fathers	34 yrs	34 yrs	34 yrs	31 yrs	33 yrs	33 yrs

Table 1 *Mean number of participants in the study by month*

	Nursery group	Family group				
	Infants	Infants	Children —6 yrs	School children 7—10 yrs	Children 11— yrs	Parents
1965 Sept.	15	33	29	33	10	[illegible]
Oct.	15	35	29	35	10	[illegible]
Nov	10	34	28	35	10	60
Dec.	16	33	28	33	10	60
1966 Jan.	17	33	7	34	8	58
Feb.	16	33	[illegible]	34	7	58
Mar	14	37	31	38	9	65
Apr	15	[illegible]	45	54	16	93
May	15		44	54	16	90
June	14	41	31	4	13	80
July	15	36	[illegible]	34	10	72
Aug	15	43	31	4	13	80
Sept.	14	49	40	30	14	66
Oct.	15	48	40	49	1	83
Nov	15	4	39	40	1	[illegible]
Dec.	17	47	30	49	11	82
1967 Jan.	10	4	38	47	10	78
Feb.	14	43	3	43	10	76
Mar	13	43	3	43	10	76
Apr	13	43	37	43	10	0
May	14	43	37	44	10	77
June	14	33	7	28	7	65
July	14	7	10	[illegible]	5	60
Aug	16	35	27	30	9	67
mean	15	40	33	40	10	73

Family population Altogether 48 families were enrolled, with a total of 277 persons (96 parents, 97 female children and 84 male children)

The children were divided into age groups according to the following principles

— Infants. All children under 2 years of age at enrolment in September 1965 or April 1966 The total number of infants was 60 33 girls and 27 boys. The mean number of infants in the study was 40.3 the weekly mean the same and the median number was 41 infants.

— Children 2—6 years of age. All children 2 years of age or older at enrolment but not in elementary school during the study period were included in this group The total number of children in this group was 47 20 girls and 27 boys. The mean number of children 2—6 years of age in the study was 30 0 the weekly mean the same and the median 32.

— School-children 7—10 years of age All children in elementary schools during the study period up to 10 years old were included in this group There were 55 children, 31 girls and 24 boys. The mean number of school children aged 7—10 years in the study was 40 6 the same as the weekly mean the median was 41

— Children 11 years old and older All the children aged 11 years or more at enrolment were in this group There were only 19 such children The mean number of older children in the study was 10 5 the weekly mean the same and the median 10 children

The mean number of parents in the study was 72.7 the mean weekly number 72.9 and the median 76

The mean monthly numbers of persons un—der observation in each of these age groups are shown in Table 1

There is a decline in the mean monthly number of participants during the summer months due to loss of children and families from observation during their vacations. Eleven families dropped out of the study 4 families because they moved out of town after participation for on av rage one year three (two of them in the beginning of the study one after 9 months) because of the laborious study procedures. Three families did not want t cooperate because of the bleedings and were released after being in the study for 4 9 and 11 months. One infant entered a day-nursery *and the family was released after 16 months* participation in the study Two persons in the ldest child group were released one was sent to a tuberculosis sanatorium, the other l ft home t study elsewhere

Description of the population

Age The mean and the median age of each study group was calculated at the beginning, *mi ldle and end of the study* The results are shown in Table 2. In the nursery group the standard deviations f the mean ages were 6½ 8½ and 7½ months, *respectively On these* occasions the youngest infants were 2 months of age, and at the end of the study the oldest infant was .. years 7 months old.

In the family infants the standard deviations of the mean ages w re 5½ *7½ and 9½* months, respectively In the families 5 infants were born during the study and at the end the oldest child in the infant group was 3½ years of age.

In the group of children aged ?—6 years, the age range was from ? *to 6 years, from* ? to 7 years and from 4 to 7 years on the 3 occasions of age estimation.

The ages *of the* school-children ranged from 5 to 10 from 6 to 11 and from 7 to 1* *years in the respective times.*

In the group of children 11 years of age or older the oldest were 18 years at the beginning of the study 1 year later one was 19 years old, but at the end of the study the ages ranged from 1.. to 17

The youngest mother was 2.. years old and the oldest 45 years when they entered the study and the youngest father was 2.. and the oldest 53 years of age.

Social grouping of the families. Most of the families belonged to the middle socioeconomic class (..) 3 families were of the *upper class* (5.8 per cent) and 13 from the

Table .. *Mea and median ages f the st dy g oups*

Study group	Ages					
	September 1 1963		September 1 1965		August 31, 1967	
	Mean	Median	Mea	Media	Mean	Median
Nursery group						
infants	9½ mo	8 mo	11 mo	3 mo	7½ mo	3 mo
Family group						
infants	9 mo	8 mo	1 yr 4½ mo	1 yr mo	2 yrs 4 mo	2 yrs mo
children 3—6 yrs	3½ yrs	3 yrs	3 yrs	4 yrs	3 yrs	3 yrs
school-children 7—10 yrs	8 yrs	8 yrs	8½ yrs	8 yrs	9½ yrs	9 yrs
children 11— yrs	14 yrs	14 yrs	12 yrs	13 yrs	14 yrs	14 yrs
mothers	33 yrs	31 yrs	32 yrs	32 yrs	32 yrs	33 yrs
fathers	34 yrs	34 yr	34 yrs	36 yrs	33 yrs	33 yrs

Table 1 *Mean number of participants in the study by month*

	Nursery group	Family group				
	Infants	Infants	Children 2—6 yrs	School-children 7—10 yrs	Children 11— yrs	Parent
1965 Sept	15	35	29	33	10	62
Oct.	15	33	29	35	10	62
Nov	16	34	28	35	10	60
Dec.	16	33	28	33	10	60
1966 Jan.	17	33	27	34	8	59
Feb.	16	33	27	34	7	58
Mar	14	37	31	38	9	65
Apr	15	54	45	54	16	93
May	13	32	44	54	16	90
June	14	41	31	42	13	80
July	15	36	26	34	10	72
Aug.	15	43	31	42	13	80
Sept	14	49	40	30	14	80
Oct	16	48	40	49	1	83
Nov	16	4	39	49	13	82
Dec.	17	47	39	49	11	83
1967 Jan.	16	43	38	47	10	78
Feb.	14	43	3	46	10	76
Mar	13	43	37	45	10	76
Apr	13	43	37	43	10	76
May	14	43	37	44	10	77
June	14	35	27	28	7	65
July	14	27	19	20	5	60
Aug	16	33	27	30	9	67
mean	15	40	33	40	10	73

Family population Altogether 48 families were enrolled, with a total of 277 persons (96 parents, 97 female children and 84 male children)

The children were divided into age groups according to the following principles

— Infants. All children under 2 years of age at enrolment in September 1965 or April 1966 The total number of infants was 60 33 girls and 27 boys. The mean number of infants in the study was 40.3 the weekly mean the same and the median number was 41 infants.

— Children 2—6 years of age. All children 2 years of age or older at enrolment but not in elementary school during the study period were included in this group The total number of children in this group was 47 20 girls and 27 boys. The mean number of children 2—6 years of age in the study was 30 0 the weekly mean the same and the median 32

— School-children 7—10 years of age All children in elementary schools during the study period up to 10 years old were included in this group There were 55 children 31 girls and 24 boys. The mean number of school children aged 7—10 years in the study was 40 6 the same as the weekly mean the median was 41

— Children 11 years old and older All the children aged 11 years or more at enrolment were in this group There were only 19 such children. The mean number of older children in the study was 10 5 the weekly mean the same and the median 10 children.

The mean number of parents in the study was 72.7 the mean weekly number 72 9 and the median 76

The mean monthly numbers of persons un ..er observation in each of these age groups are shown in Table 1

There is a decline in the mean monthly number of participants during the summer months due to loss of children and families from observation during their vacations. Eleven families dropped out of the study 4 families because they moved out of town after participation for on average one year three (two of them in the beginning of the study one after 9 months) because of the laborious study procedures. Three families did not want to cooperate because of the bleedings and were released after being in the study for 4 9 and 11 months. One infant entered a day-nursery and the family was released after 16 months participation in the study. Two persons in the oldest child group were released one was sent to a tuberculosis sanatorium, the other left home t study elsewhere.

Description of the population

Age. The mean and the median age of each study group was calculated at the beginning, middle and end of the study. The results are shown in Table .. In the nursery group the standard deviations of the mean ages were 5½ 8½ and 7½ months, respectively. On these occasions the youngest infants were .. months of age, and at the end of the study the oldest infant was ? years 7 months old.

In the family infants the standard deviations of the mean ages were 5½ 7½ and 9½ months, respectively. In the families 5 infants were born during the study and at the end the oldest child in the infant group was 3½ years of age.

In the group of children aged ..—6 years, the age range was from ? to 6 years, from to 7 years and from 4 to 7 years on the 3 occasions of age estimation.

The ages of the school-children ranged from 5 to 10, from 6 to 11 and from 7 to 1 years in the respective times.

In the group of children 11 years of age or older the oldest were 18 years at the beginning of the study 1 year later one was 19 years old, but at the end f the study the ages ranged from 1? to 17

The youngest mother was .. years old and the oldest 45 years when they entered the study and the youngest father was 25 and the oldest 53 years of age.

Social grouping of the f milies. Most of the families belonged to the middle socioeconomic class (55) 3 families were of the upper class (5.8 per cent) and 13 from the

Table .. *Mean and m dian ages f the st dy g oups*

Study group	Ages					
	September 1 1963		September 1 1966		August 31, 1967	
	Mean	Median	Mean	Median	Mean	Median
Nursery group						
infants	9½ mo	8 mo	11 mo	3 mo	7½ mo	3 mo
Family group						
infants	9 mo	8 mo	1 yr 4½ mo	1 yr 3 mo	2 yrs 4 mo	2 yrs 5 mo
children —6 yr	3½ yrs	3 yrs	3 yrs	4 yrs	3 yrs	3 yrs
school children 7—10 yrs	8 yrs	8 yrs	8½ yrs	8 yrs	9½ yrs	9 yrs
children 11— yrs	14 yrs	14 yrs	17 yrs	13 yrs	14 yrs	14 yrs
mothers	33 yrs	31 yrs	33 yrs	33 yrs	33 yrs	33 yrs
fathers	34 yrs	34 yrs	34 yrs	34 yrs	35 yrs	35 yrs

lower class (29.2 per cent) Usually the homes were clean and good care was taken of the children Twenty-eight families lived in modern flats, but some of these were rather small for the size of the family Four families had houses of their own. Sixteen families lived in definitely overcrowded conditions. Some of these homes were in old frame-houses not supplied with modern conveniences. Four of these families moved to better quarters during the study period. In 7 families the care of the children was not adequate as was indicated by the fact that the children were not properly clothed, dental care was neglected and the diet was not well balanced.

Nine of the mothers were in full time employment outside the home and 8 were in occasional or part time employment.

Residence of the families The families in the study mainly resided in 4 areas within a distance of 2 miles from the hospital In the beginning of the study one-third lived in the central city area the others were living in 3 housing estates in the other side of the hospital which is situated on the border of the central city area. Four of the families moved to new housing areas far from the hospital but remained in the study

After April 1966 when the new group of families was recruited, one-third still lived in the central city area. Almost one-third of the families now resided in each of the other two housing estates. During the last year of the study the people from the central city area moved to the third housing estate and some dropped out of the study At the end the families were distributed evenly in the central city area and the 3 housing estates at the outer edge of the city

Size of the families. Half of the 48 families included in the study consisted of 5 members, 16 families had 6 members, 4 had 7 members, 3 had 8 and one family had 9 members.

School attendance The mean number of children attending nursery play groups was 6 and kindergarten 9 The mean number of children in elementary public schools was the highest number being 45 in fall 1966. average 7 of the children in the family gr were attending high schools.

Of the oldest children 3 were already work.

Medical status In the nursery group th were 2 premature infants, 4 with congen malformations, 2 microcephalics, one menta retarded with a cleft palate and one inf with paralysis of the lower extremities, w had been operated on for hydrocephal These last two infants stayed for the long times in the nursery Of the infants in t *family group* 4 had atopic dermatitis, one h congenital heart disease and one had congenital malformation of the urinary trac One child aged 2 years had atopic dermatiti Of the school-children one had asthma an one was a diabetic One of the fathers ha congenital heart disease

Previous communicable diseases of childhood Histories of these diseases were elicite only in the family group Of the infants one had had measles, 2 varicella and one mumps In the children 2—6 years of age there had been 11 cases of measles, 3 cases of rubella, 10 cases of varicella and 4 cases of mumps. Of the school-children 38 had had measles, 4 rubella 34 varicella and 21 mumps. Of the oldest children 14 had had measles, 3 rubella, 11 varicella, 11 mumps and one scarlet fever Measles had occurred in 35 per cent of all children, rubella in 4 per cent varicella in 32 per cent and mumps in 20 per cent.

Duration of observation

Nursery group The total observation time of the infants in the nursery group was 342 person-months, resulting in mean obser- vation period of 6 0 months infant. One infant was resident for the observation period of 2 years.

Family group The total observation time

of infants was 1031 person-months, resulting in a mean observation of 17 months per infant. The children aged from 2 to 6 years were observed for a total of 864 person-months, 18 months per child. The total observation time for schools-children was 1041 person-months, averaged 19 months per child. The oldest children were under observation for 264 person-months, 14 months per child. The total person-months of observation were 4977 for the family group, including the vacation periods.

STUDY PROCEDURE

The surveillance was carried out from September 1 1965 to August 31, 1967

Methods of observation

At the start of the study all the children were examined by the autho at child welfare centers The examination was repeated in summer 1966 and 1967 Home visits were made by the author 3 times a year to all families from which no respiratory illnesses had been recently reported.

The aim was to study all acute respiratory illnesses which occurred among the partici pants. No daily health records were kept in the families. The mothers were asked to con tact the author by telephone when respiratory symptoms occurred in any member of the family The mothers kept records of symptoms until the patient was healthy The parents were not observed so closely as the children, but were asked to report their respiratory illnesses, particularly when other members of the family had respiratory symptoms at the same time.

In the nursery the rectal temperature of each child was measured twice a day Careful records were kept of all respiratory and other symptoms of illness. Acute respiratory illnesses were immediately reported to the author

Collection of specimens

When a new case of respiratory illness was reported, the members of the family group were seen at the outpatient clinic of the Children s Hospital or sometimes, when older children were ill, the specimens were collected at home. All the specimens from the infants of the nursery group were taken in the nursery

Pharyngeal swabs for virus isolation were taken from each patient with respiratory symptoms. The pharynx was firmly swabbed with 4 cotton applicators as described by Berglund *et al.* (10) From the infants of the nursery group rectal swabs were also collected from April 1966 onwards.

Acute and convalescent phase blood samples were collected during each respiratory illness. All blood samples were obtained by veni puncture, in the older infants, children and adults from cubital veins, in the youngest infants from scalp veins. The blood (5 ml) was allowed to drip from the needle to the centrifuge tube. The convalescent phase blood sample was taken 10—14 days after the acute phase sample except in infants, where the period was 14—21 days. Supplementary blood samples were sometimes taken in the nursery group 4—6 weeks after the onset of the illness if the infant was very young, and delay of the antibody response was suspected (7) During an epidemic of *RS* virus in the nursery described elsewhere (29) when the middle ear aspirates from infants with otitis media were cultured for isolation of viruses and bacteria, the infants were bled simulta neously with the ear-drum punctures. The convalescent phase blood samples were taken on home visits more often than the acute phase samples.

In cases in which a second acute respiratory infection followed immediately after the first, a single blood sample served as the convales cent phase sample for the first and as the acute phase sample for the second illness

lower class (29.2 per cent) Usually the homes were clean and good care was taken of the children Twenty-eight families lived in modern flats, but some of these were rather small for the size of the family Four families had houses of their own. Sixteen families lived in definitely overcrowded conditions. Some of these homes were in old frame-houses not supplied with modern conveniences. Four of these families moved to better quarters during the study period. In 7 families the care of the children was not adequate, as was indicated by the fact that the children were not properly clothed, dental care was neglected and the diet was not well balanced

Nine of the mothers were in full time employment outside the home and 8 were in occasional or part time employment.

Residence of the families The families in the study mainly resided in 4 areas within a distance of 2 miles from the hospital In the beginning of the study one-third lived in the central city area the others were living in 3 housing estates in the other side of the hospital which is situated on the border of the central city area. Four of the families moved to new housing areas far from the hospital but remained in the study

After April 1966 when the new group of families was recruited, one-third still lived in the central city area. Almost one-third of the families now resided in each of the other two housing estates. During the last year of the study the people from the central city area moved to the third housing estate and some dropped out of the study At the end the families were distributed evenly in the central city area and the 3 housing estates at the outer edge of the city

Size of the families Half of the 48 families included in the study consisted of 5 members, 16 families had 6 members, 4 had 7 members, 3 had 8 and one family had 9 members.

School attendance The mean number of children attending nursery play groups was 6 and kindergarten 9 The mean number of children in elementary public schools was 3 the highest number being 45 in fall 1966 O average 7 of the children in the family grou were attending high schools.

Of the oldest children 3 were already a work.

Medical status In the nursery group ther were 2 premature infants, 4 with congenita malformations, 2 microcephalics, one mentally retarded with a cleft palate and one infan with paralysis of the lower extremities, who had been operated on for hydrocephalus These last two infants stayed for the longest times in the nursery Of the infants in the family group 4 had atopic dermatitis, one had congenital heart disease and one had a congenital malformation of the urinary tract. One child aged 2 years had atopic dermatitis. Of the school-children one had asthma and one was a diabetic One of the fathers had congenital heart disease.

Previous communicable diseases of childhood Histories of these diseases were elicited only in the family group Of the infants one had had measles, 2 varicella and one mumps. In the children 2—6 years of age there had been 11 cases of measles, 3 cases of rubella 10 cases of varicella and 4 cases of mumps. Of the school-children 38 had had measles, 2 rubella 34 varicella and 21 mumps. Of the oldest children 14 had had measles, 3 rubella 11 varicella, 11 mumps and one scarlet fever Measles had occurred in 35 per cent of all children, rubella in 4 per cent varicella in 32 per cent and mumps in 20 per cent.

Duration of observation

Nursery group The total observation time of the infants in the nursery group was 342 person-months, resulting in a mean observation period of 6 0 months per infant. One infant was resident for the whole observation period of 2 years.

Family group The total observation time

infants was 1031 person-months, resulting mean observation of 17 months per infant. The children aged from 2 to 6 years were observed for a total of 864 person-months, 18 months per child. The total observation time for schools-children was 1041 person-months, averaged 19 months per child. The oldest children were under observation for 264 person-months, 14 months per child. The total person-months of observation were 4977 for the family group including the vacation periods.

STUDY PROCEDURE

The surveillance was carried out from September 1 1963 to August 31 1967

Methods of observation

At the start of the study all the children were examined by the author at child welfare centers. The examination was repeated in summe 1966 and 1967 Home visits were made by the author 3 times a year to all families from which no respiratory illnesses had been resently reported.

The aim was to study all acute respiratory illnesses which occurred among the participants. No daily health records were kept in the families. The mothers were asked to contact the author by telephone when respiratory symptoms occurred in any member of the family The mothers kept records of symptoms until the patient was healthy The parents were not observed so closely as the children, but were asked to report their respiratory illnesses, particularly when other members of the family had respiratory symptoms at the same time

In the nursery the rectal temperature of each child was measured twice a day Careful records were kept of all respiratory and other symptoms of illness. Acute respiratory illnesses were immediately reported to the autho

Collection of specimens

When a new case of respiratory illness was reported, the members of the family group were seen at the outpatient clinic of the Children's Hospital or sometimes, when older children were ill, the specimens were collected at home. All the specimens from the infants of the nursery group were taken in the nursery

Pharyngeal swabs for virus isolation were taken from each patient with respiratory symptoms. The pharynx was firmly swabbed with 4 cotton applicators as described by Berglund *et al.* (10) From the infants of the nursery group rectal swabs were also collected from April 1966 onwards.

Acute and convalescent phase blood samples were collected during each respiratory illness. All blood samples were obtained by veni puncture, in the older infants, children and adults from cubital veins, in the youngest infants from scalp veins. The blood (5 ml) was allowed to drip from the needle to the centrifuge tube. The convalescent phase blood sample was taken 10—14 days after the acute phase sample except in infants, where the period was 14— 1 days. Supplementary blood samples were sometimes taken in the nursery group 4—6 weeks after the onset of the illness if the infant was very young, and delay of the antibody response was suspected (7) During an epidemic of RS virus in the nursery described elsewhere (29) when the middle ear aspirates from infants with otitis media were cultured for isolation of viruses and bacteria, the infants were bled simultaneously with the ear-drum punctures. The convalescent phase blood samples were taken on home visits more often than the acute phase samples.

In cases in which a second acute respiratory infection followed immediately after the first, a single blood sample served as the convalescent phase sample for the first and as the acute phase sample for the second illness.

lower class (29.2 per cent) Usually the homes were clean, and good care was taken of the children Twenty-eight families lived in modern flats, but some of these were rather small for the size of the family Four families had houses of their own. Sixteen families lived in definitely overcrowded conditions. Some of these homes were in old frame-houses not supplied with modern conveniences. Four of these families moved to better quarters during the study period. In 7 families the care of the children was not adequate as was indicated by the fact that the children were not properly clothed, dental care was neglected and the diet was not well balanced.

Nine of the mothers were in full time employment outside the home and 8 were in occasional or part time employment.

Residence of the families The families in the study mainly resided in 4 areas within a distance of 2 miles from the hospital In the beginning of the study one-third lived in the central city area the others were living in 3 housing estates in the other side of the hospital, which is situated on the border of the central city area. Four of the families moved to new housing areas far from the hospital, but remained in the study

After April 1966 when the new group of families was recruited one-third still lived in the central city area. Almost one-third of the families now resided in each of the other two housing estates. During the last year of the study the people from the central city area moved to the third housing estate and some dropped out of the study At the end the families were distributed evenly in the central city area and the 3 housing estates at the outer edge of the city

Size of the families Half of the 48 families included in the study consisted of 5 members, 16 families had 6 members, 4 had 7 members, 3 had 8 and one family had 9 members.

School attendance The mean number of children attending nursery play groups was 6 and kindergarten 9 The mean number of children in elementary public schools was 3 the highest number being 45 in fall 1966 On average 7 of the children in the family group were attending high schools.

Of the oldest children 3 were already at work.

Medical status In the nursery group there were 2 premature infants, 4 with congenital malformations, 2 microcephalics, one mentally retarded with a cleft palate and one infant with paralysis of the lower extremities, who had been operated on for hydrocephalus. These last two infants stayed for the longest times in the nursery Of the infants in the family group 4 had atopic dermatitis, one had congenital heart disease and one had a congenital malformation of the urinary tract. One child aged 2 years had atopic dermatitis. Of the school-children one had asthma and one was a diabetic. One of the fathers had congenital heart disease.

Previous communicable diseases of childhood Histories of these diseases were elicited only in the family group Of the infants one had had measles, 2 varicella and one mumps. In the children 2—6 years of age there had been 11 cases of measles, 3 cases of rubella 10 cases of varicella and 4 cases of mumps. Of the school-children 38 had had measles, 2 rubella 34 varicella and 21 mumps. Of the oldest children 14 had had measles, 3 rubella, 11 varicella 11 mumps and one scarlet fever Measles had occurred in 35 per cent of all children rubella in 4 per cent varicella in 32 per cent and mumps in 20 per cent.

Duration of observation

Nursery group The total observation time of the infants in the nursery group was 342 person-months, resulting in a mean observation period of 6.0 months per infant. One infant was resident for the whole observation period of 2 years.

Family group The total observation time

nts or re-examinations at the outpatient were performed. The mothers were structed to measure the temperatures of e patients until they had returned to nor al. The patient was considered to be cured hen all signs of respiratory illness had isappeared.

On the convalescent phase visit the history f the current illness was obtained, the patient xamined to ensure that no signs of respira ory illness remained and the final clinical liagnosis was made. The diagnostic criteria aid down by Tyrrell (69) and commonly accepted in pediatric practice were used to lassify the acute respiratory illnesses.

The length of the respiratory illness was mostly based on the persistence of nasal discharge, particularly in infants. Fairly often during such periods, exacerbation in the respiratory symptoms occurred. In such cases it was taken as a new illness and marked termi nation of the preceding illness, although no return to complete health had occurred.

Data processing

The basic information on each participant was coded on an IBM card. For each respiratory illness another IBM card was prepared, containing personal identification data, dates of onset of illness, recovery and sampling, results of virus isolation, coded clinical diagnosis, information on temperature, signs and symptoms and the CF results. The results of HI and neutralization test with 4-fold or greater rise in antibody titer were recorded on a separate card. For information on other than respiratory illnesses observed during the study an additional card was prepared, containing the date and coded clinical diagnosis of the illness.

The data were processed at the Institute f Applied Mathematics, University of Turku, with an IBM 1130 Computer rented from IBM. The computer was programed to search for significant serologic rises (4-fold or greater rise of antibody titer in CF, HI or neutralization tests) and to combine these with relevant virus isolations. Each respiratory illness was thus labeled with the specific virus etiology.

The weekly and total numbers of new cases of respiratory illnesses adequately studied were counted from the dates of obtaining the pharyngeal swabs. The duration of the respiratory illness was calculated by the computer from the dates of onset and recovery. The computer selected the data of the acute respiratory infections to obtain the other information presented.

The computer was also programed to calculate the ages of the study population and the weekly mean numbers of participants from the data on the basic personal information cards. The mean weekly percentages of individuals with respiratory symptoms were calculated by the computer from the dates of onset and recovery and the mean weekly numbers of participants.

Statistical methods

The degree of statistical significance has been determined by Student's t-test and chi square test. The IBM computer performed the chi-square tests. The difference between proportions is said to be almost significant, if $0.01 < p \geq 0.05$, significant if $0.001 < p \geq 0.01$ and highly significant, if $p \geq 0.001$

LABORATORY METHODS

Cell cultures

The cell cultures used for virus isolation were HeLa, U (continuous human amnion cell line) and primary monkey kidney cells. Their origin and the techniques used with these cells have been described in detail by Minty

Table 3 *Specimens collected*

Study group	Number of specimens				
	Virus isolation		Serum		
	Pharyngeal swabs	Rectal swabs	Acute phase	Convalescent	Supplementary
Nursery group					
infants	180	1 3	1 0	181	31
Family group					
infants	209	1	190	203	—
children 2—6 yrs	106	2	104	110	—
school-children 7—10 yrs	33	—	56	57	—
children 11— yrs	7	—	7	7	—
parents	24	—	32	33	—
Total	600	123	359	393	31

Rectal swab specimens were also taken from a few patients of the family group with respiratory illness accompanied with diarrhea Table 3 shows the total numbers of specimens. A convalescent phase blood sample was sometimes not available. Some specimens were contaminated and in addition, a few were lost during laboratory processing

All the serum specimens were tested by the complement fixation (CF) technique using the following antigens RS virus, parainfluenza viruses types 1 2 and 3 influenza viruses types A and B mumps virus, adenovirus group herpes simplex and *M pneumoniae* The other serologic tests performed were based on isolations of viruses and epidemiologic findings. Nearly all sera were tested in the hemagglutination inhibition (HI) test for antibodies to adenovirus types 1 2 and 5 With adenovirus types 6 3 and 7 HI tests were performed on fewer specimens, mostly only when these viruses had been isolated. Paired sera with a rise or high titer of parainfluenza virus antibodies in the CF test were examined in the HI test for antibodies to parainfluenza types 1 2 and 3 Similarly sera with an influenza A antibody rise in the CF test were tested in HI to influenza A2 antibody

The sera from patients with RS virus isolations but no rise in the CF test to RS antibody were tested by neutralization with RS virus. Likewise, the paired sera showing 2 fold rise in RS antibody in the CF test were tested by neutralization Neutralization test with Coxsackie B5 and ECHO 9 viruses were restricted to individuals with these isolations and their immediate contacts. The sera from patients with Coxsackie B type 2 isolation and their contacts were tested in the CF test against Coxsackie B type 1 –5

Clinical examination

On the visit at the acute phase of the disease a careful medical history was taken and a clinical examination performed Upon initial examination the respiratory illnesses were clinically diagnosed and if necessary chest roentgenograms and laboratory tests were taken. The children with otitis media were sent to otologist. The necessary medication was prescribed. Some seriously ill children were remitted to hospital.

The course of the illnesses was followed The staff in the nursery and the mothers kept in contact by telephone and often home

visits or re-examinations at the outpatient clinic were performed. The mothers were instructed to measure the temperatures of the patients until they had returned to normal. The patient was considered to be cured when all signs of respiratory illness had disappeared.

On the convalescent phase visit the history of the current illness was obtained, the patient examined to ensure that no signs of respiratory illness remained and the final clinical diagnosis was made. The diagnostic criteria laid down by Tyrrell (69) and commonly accepted in pediatric practice were used to classify the acute respiratory illnesses.

The length of the respiratory illness was mostly based on the persistence of nasal discharge, particularly in infants. Fairly often during such periods, exacerbation in the respiratory symptoms occurred. In such cases it was taken as a new illness and marked termination of the preceding illness, although no return to complete health had occurred.

Data processing

The basic information on each participant was coded on an IBM card. For each respiratory illness another IBM card was prepared, containing personal identification data, dates of onset of illness, recovery and sampling, results of virus isolation, coded clinical diagnosis, information on temperature, signs and symptoms and the CF results. The results of HI and neutralization test with 4-fold or greater rise in antibody titer were recorded on a separate card. For information on other than respiratory illnesses observed during the study an additional card was prepared, containing the date and coded clinical diagnosis of the illness.

The data were processed at the Institute of Applied Mathematics, University of Turku, with an IBM 1130 Computer rented from IBM. The computer was programed to search for significant serologic rises (4-fold or greater rise of antibody titer in CF, HI or neutralization tests) and to combine these with relevant virus isolations. Each respiratory illness was thus labeled with the specific virus etiology.

The weekly and total numbers of new cases of respiratory illnesses adequately studied were counted from the dates of obtaining the pharyngeal swabs. The duration of the respiratory illness was calculated by the computer from the dates of onset and recovery. The computer selected the data of the acute respiratory infections to obtain the other information presented.

The computer was also programed to calculate the ages of the study population and the weekly mean numbers of participants from the data on the basic personal information cards. The mean weekly percentages of individuals with respiratory symptoms were calculated by the computer from the dates of onset and recovery and the mean weekly numbers of participants.

Statistical methods

The degree of statistical significance has been determined by Student's t-test and chi-square test. The IBM computer performed the chi-square tests. The difference between proportions is said to be almost significant, if $0.01 < p \leqq 0.05$, significant if $0.001 < p \leqq 0.01$ and highly significant, if $p \leqq 0.001$.

LABORATORY METHODS

Cell cultures

The cell cultures used for virus isolation were HeLa, U (continuous human [illegible] cell line) and primary monkey kidney cells. Their origin and the techniques used [illegible] these cells have been [illegible]

jarvi (44) GMK and LLC-MK₂ cell cultures were used in enterovirus neutralization tests and in CF antigen preparations.

The growth medium for HeLa cells consisted of 55 per cent Hanks's balanced salt solution, 30 per cent inactivated human serum and 15 per cent tryptose phosphate broth (TPB) (Difco, distributed by Microbiological Laboratory Laaketehdas Orion Oy Helsinki, Finland) The growth medium for U cells consisted of 75 per cent lactalbumin hydrolysate (LAH) (Nutritional Biochemical Corporation Cleveland, Ohio) in Hanks's solution in a final concentration of 5 mg LAH/l and 25 per cent inactivated calf serum The inoculum was 100 000 HeLa and U cells per tube. The maintenance medium (44) of HeLa and U cells consisted of Eagle's minimum essential medium (MEM) supplemented with 5 per cent inactivated horse serum and 5 per cent TPB However for rectal swab specimens the maintenance medium of U cells consisted of Parker's medium 199 (Parker) supplemented with 0.1 per cent bovine serum albumin (Bovine serum albumin fraction V Armour Pharmaceutical Co distributed by Microbiological Laboratory Laaketehdas Orion Oy Helsinki Finland) From June 1966 this medium was changed to MEM supplemented with 2 per cent inactivated chicken serum.

Primary monkey kidney cells were obtained from the State Bacteriological Laboratory Stockholm, Sweden. They were grown in a medium consisting of 70 per cent LAH solution, 20 per cent inactivated calf serum and 10 per cent TPB The maintenance medium was Parker with 0 1 per cent bovine serum albumin.

GMK cells (a continuous line of African green monkey kidney cells) were obtained from Dr Arne Svedmyr Central Bacteriological Laboratory Stockholm City Stockholm, Sweden The growth medium consisted of 89 per cent MEM 10 per cent inactivated calf serum and 1 per cent L-arginine solution (1 74 gm/l) The GMK cultures were treated as HeLa and U cell cultures (44) Dur[ing] a growth period of two weeks the medi[um] was replaced once and a one-liter Roux bott[le] yielded 80 tissue culture tubes. GMK ce[lls] were maintained in 97 per cent MEM with [1] per cent inactivated calf serum, 1 per ce[nt] L-arginine solution (1 74 gm/l) and addi[]tional 0 1 per cent dextrose

LLC-MK₂ cells (a continuous line [of] monkey kidney cells) were obtained from th[e] National Institutes of Health, Bethesda, M[d.] The growth medium consisted of basal mediu[m] (Eagle) Diploid (BME) (Grand Island Bi[o]logical Company Grand Island, New York) with 10 per cent inactivated calf serum. Ce[lls] grown in a Roux bottle were treated wit[h] 10 ml of 0.25 per cent trypsin in Hanks solution, the trypsin was decanted and th[e] bottle was incubated at 37°C for 10—15 mi[n.] Then the cells were suspended in the growt[h] medium and 80 tissue culture tubes wer[e] inoculated from one Roux bottle. The main[]tenance medium consisted of BME Diploi[d] supplemented with 1 per cent inactivate[d] fetal calf serum (Microbiological Laboratory Lääketehdas Orion Oy Helsinki, Finland)

The maintenance media contained 40[0] units/ml penicillin, 400 μg/ml streptomycin 25 units/ml mycostatin and 5 μg/ml amphotericin B All tissue culture media contained 0 002 per cent phenol red The pH was adjusted with 7 per cent NaHCO

Virus isolation

The pharyngeal and rectal swab specimens were inoculated directly into tissue culture tubes by the technique described in detail by Berglund *et al* (10) Duplicate cultures in HeLa U and primary monkey kidney cells were inoculated by one cotton applicator per cell line. The tissue culture tubes used for direct inoculation contained ‑ ml of maintenance medium instead of the regular 1 ml to prevent drying of cells during transport.

ne of the applicators was placed in a tube ontaining ml Hanks's solution with 0.1 % ovine albumin, 500 units penicillin/ml, 500 g streptomycin/ml, 25 units mycostatin/ml nd 5 μg amphotericin B/ml. This tube was tored at —60°C.

The cultures of the pharyngeal swab speci nens were incubated in stationary racks at 35 C and those of the rectal swab specimens t 37°C. In the beginning of the study the naintenance medium was changed every 5th lay but after spring 1966, it was changed twice a week. The HeLa cell cultures were maintained 12—14 days and when sponta neous degeneration of cells occurred a blind passage was made. In U and monkey kidney cells the cultures were usually maintained for 14 days. The cultures were examined for cytopathogenic effect (CPE) every second lay. When CPE was suspected, a second passage was made. The monkey kidney cell ultures were tested for hemadsorption with human type O erythrocytes at 4 C on the 5th and 10th days.

The isolated viruses were identified accord ing to the following procedures.

The isolates showing syncytial CPE were tested in complement fixation (CF) reaction using paired sera from patients with at least 10-fold antibody rise to respiratory syncytial (RS) virus (10).

The isolates positive in hemadsorption and with hemagglutinating activity were identified by the hemagglutination inhibition (HI) test, using anti parainfluenza virus guinea pig sera and anti-influenza A2 rabbit sera. Some of the hemadsorbing isolates failed to agglutinate sufficiently. These were identified by neutral ization with the parainfluenza virus immune sera r by the CF reaction, using paired patient sera with an antibody rise to influenza A virus.

The adenovirus isolates were identified by the presence of adenovirus group-specific antigen in the CF test (44). The adenovirus types were identified by the HI test with type-specific immune rabbit sera. Herpes simplex viruses were identified by the neutralization test, using an immune rabbit serum (45).

The isolates which could not be typed by the above-described methods were subjected to neutralization tests with enterovirus anti-sera acquired from the Wellcome Research Laboratories, Beckenham, England (Coxsackie B type 5 ECHO 6 9) and from the National Institutes of Health, Bethesda, Md. (Coxsackie B type 1—4). The typing results of one para influenza type 1 strain, and two Coxsackie B type 5 strains and three ECHO 9 strains were kindly confirmed at the Respirovirus Unit and Enterovirus Infection Unit at the National Communicable Disease Center Atlanta, Georgia.

Serologic methods

Complement fixation test

Procedure. The microtechnique of Sever (61) was used. Veronal — buffered diluent (VBD) with 0.1 per cent gelatine was used as diluent (30). Complement was fresh pooled guinea pig serum stored in small volumes at —60°C.

The hemolytic system consisted of equal parts of 2 per cent sheep erythrocytes and a dilution of hemolysin containing two full units. The tests were performed with 3—4 units of antigen. After addition of the hemolytic system, the plates were incubated at 37°C for 1 hour and shaken by hand every 15 min. Then the plates were placed at 4 C for 1—2 hours and read by visual estimation of the degree of hemolysis. The inhibition of hemolysis was recorded from 4+ to — and readings of 4+ and 3+ were considered positive.

A control complement titration in the presence of each antigen, the serum controls and the titration of a known positive serum for each antigen were included in each series of CF tests. All the sera of one patient were examined in the same series of CF tests.

Antigens All tissue culture antigens were prepared in Roux bottles and harvested when the cells showed complete CPE usually on the 4th to 7th day after inoculation The cells were detached and disrupted by freezing and thawing

Adenovirus antigen was prepared from adenovirus type 5 in HeLa cells (44) The HeLa maintenance medium containing horse serum was used. RS virus antigen was prepared with the Randall strain in U cells with the maintenance medium supplemented with horse serum (10) Parainfluenza virus antigens types 2 and 3 (strains obtained from WHO International Reference Centre for Respiratory Virus Diseases, Harvard Hospital Salisbury Wilts) were prepared in U cells. The maintenance medium contained MEM supplemented with 5 per cent horse serum

Parainfluenza virus type 1 mumps and influenza antigens were obtained from the State Serum Institute Helsinki Finland. Parainfluenza virus type 1 antigen was a Sendai antigen in allantoic fluid from embryonated eggs. The mumps antigen was also in allantoic fluid and was prepared with the Enders strain Influenza A2 antigen was prepared with strain influenza A2/Singapore/57 and influenza B antigen with influenza B/Lee strain both in allantoic fluids.

Mycoplasma pneumoniae (Eaton PPLO) antigen was kindly supplied by Dr Elli Jansson Municipal Bacteriologic Laboratory Aurora Hospital Helsinki Finland (36)

Herpes simplex antigen was prepared in HeLa cells or in human fibroblast cultures. The maintenance medium for HeLa cells was supplemented with horse serum Human fibroblasts were grown in MEM supplemented with 10 per cent inactivated calf serum the maintenance medium was the same with 3 per cent inactivated calf serum

Antigens to Coxsackie B types 1—5 were prepared in U cells. The maintenance medium was MEM supplemented with 5 per cent horse serum.

Hemagglutination inhibition test

Procedure The hemagglutination and hemagglutination inhibition tests were performed by the microtitration method of Sever (61) with the following modifications. Phosphate buffered saline was used at dilution Disposable microtiter U plates (Linbro Chemical Co Inc., New Haven Conn) were used in all HI tests. The volume of the antigen and serum dilutions was 0 025 ml, and the volume of erythrocyte suspensions 0 05 ml

In HI tests, 4 antigen units were used. The test was incubated 1 hour at room temperature before the erythrocytes were added. All sera from one patient were included in the same HI test

Adenoviruses. Rat and monkey erythrocytes were used. The rat erythrocytes were obtained by heart puncture from rats of Long Evans strain The African green monkey erythrocytes were obtained from State Bacteriological Laboratory Stockholm Sweden The erythrocytes were washed three times with phosphate buffered saline and stored as a 10 per cent suspension in Alsever's solution (13) The erythrocytes were used as a 0 5 per cent suspension The rat erythrocytes were suspended in 1 100 dilution of normal rabbit serum (56)

The adenovirus HA antigens of types 1—7 were produced by the same method as the adenovirus CF antigen For the antigens of types 1 2 and 5 a 1 100 dilution of type 6 immune serum was used as diluent to make agglutination complete (56) Similarly for type 6 antigen a dilution of type 2 immune serum was used

The sera were adsorbed with kaolin and rat and monkey erythrocytes by the method described by Halonen *et al* (31) and heat inactivated at 56 C for 30 min After the erythrocytes were added, the plates were incubated at 37 C for 1 hour

Parainfluenza viruses Human type O erythrocytes were used They were treated

described above with rat erythrocytes and used as a 0.4 per cent suspension.

The parainfluenza virus type 1 antigen was the same Sendai antigen as in the CF test. The type 2 and 3 antigens were prepared in U cells. The maintenance medium was Parker supplemented with 0._ per cent bovine serum albumin.

The sera were treated with M/90 potassium periodate (22) and heat-inactivated at 56°C for 30 min. When the erythrocyte suspension was added, the plates were incubated at room temperature.

Influenza A2 virus. Chicken erythrocytes were treated in the same way as rat erythrocytes and used as a 0.5 per cent suspension.

The influenza A_ antigen was in allantoic fluid harvested from embryonated eggs after inoculation with influenza A2/Finland/1/65 strain obtained from the State Serum Institute, Helsinki, Finland.

The treatment of sera and the test procedure were the same as for parainfluenza virus III test.

Neutralization test

Procedure. All viruses were diluted to contain approximately 100 TCD_{50} units of virus per 0.1 ml. The sera were inactivated at 56°C for 30 min. The patient sera were diluted 2 fold from the initial dilution of 1:4. The virus and serum dilutions in equal volumes were mixed, incubated as described later and inoculated in 0.2 ml volumes into duplicate tissue culture tubes. A control titration of the virus was always included in the test. The test was read when control tubes showed a CPE of 3+ to 4+. The titer was the highest serum dilution with a CPE of 1+ or less. All the sera from one patient were included in the same neutralization test.

RS virus. The RS virus strain used in the neutralization tests was a patient strain from this study. It had been identified by the CF method (9). The test was performed in U cells. The incubation time for virus-serum mixture was 1 hour at room temperature. The tissue culture medium was changed on the day following inoculation.

Coxsackie B type 5 virus. The serum-virus mixture was incubated 2 hours at 37°C (48). The isolates were typed by neutralization in GMK cells. The neutralization tests of patient sera were performed in LLC-MK cells.

ECHO 9 virus. The maintenance medium was BME Diploid with 1 per cent fetal calf serum. The isolates were typed in GMK cells, the serum neutralizations performed in LLC-MK_2 cells. The procedure was the same as in the Coxsackie B type 5 neutralization.

Antigens All tissue culture antigens were prepared in Roux bottles and harvested when the cells showed complete CPE usually on the 4th to 7th day after inoculation The cells were detached and disrupted by freezing and thawing

Adenovirus antigen was prepared from adenovirus type 5 in HeLa cells (44) The HeLa maintenance medium containing horse serum was used RS virus antigen was prepared with the Randall strain in U cells with the maintenance medium supplemented with horse serum (10) Parainfluenza virus antigens types 2 and 3 (strains obtained from WHO International Reference Centre for Respiratory Virus Diseases, Harvard Hospital Salisbury Wilts) were prepared in U cells. The maintenance medium contained MEM supplemented with 5 per cent horse serum

Parainfluenza virus type 1 mumps and influenza antigens were obtained from the State Serum Institute Helsinki Finland Parainfluenza virus type 1 antigen was a Sendai antigen in allantoic fluid from embryonated eggs. The mumps antigen was also in allantoic fluid and was prepared with the Enders strain Influenza A2 antigen was prepared with strain influenza A2/Singapore/57 and influenza B antigen with influenza B/Lee strain both in allantoic fluids.

Mycoplasma pneumoniae (Eaton PPLO) antigen was kindly supplied by Dr Elli Jansson Municipal Bacteriologic Laboratory Aurora Hospital Helsinki Finland (36)

Herpes simplex antigen was prepared in HeLa cells or in human fibroblast cultures. The maintenance medium for HeLa cells was supplemented with horse serum Human fibroblasts were grown in MEM supplemented with 10 per cent inactivated calf serum the maintenance medium was the same with 3 per cent inactivated calf serum

Antigens to Coxsackie B types 1—5 were prepared in U cells. The maintenance medium was MEM supplemented with 5 per cent horse serum

Hemagglutination inhibition test

Procedure The hemagglutination and hemagglutination inhibition tests were performed by the microtitration method of Sever (61) with the following modifications. Phosphate-buffered saline was used at diluent Disposable microtiter U plates (Linbro Chemical Co Inc. New Haven Conn) were used in all HI tests. The volume of the antigen and serum dilutions was 0 025 ml and the volume of erythrocyte suspensions 0 05 ml.

In HI tests, 4 antigen units were used The test was incubated 1 hour at room temperature before the erythrocytes were added. All sera from one patient were included in the same HI test

Adenoviruses Rat and monkey erythrocytes were used. The rat erythrocytes were obtained by heart puncture from rats of Long Evans strain The African green monkey erythrocytes were obtained from State Bacteriological Laboratory Stockholm Sweden The erythrocytes were washed three times with phosphate-buffered saline and stored as a 10 per cent suspension in Alsever's solution (13) The erythrocytes were used as a 0.5 per cent suspension The rat erythrocytes were suspended in 1 100 dilution of normal rabbit serum (56)

The adenovirus HA antigens of types 1—7 were produced by the same method as the adenovirus CF antigen For the antigens of types 1 2 and 5 a 1 100 dilution of type 6 immune serum was used as diluent to make agglutination complete (56) Similarly for type 6 antigen a dilution of type 2 immune serum was used.

The sera were adsorbed with kaolin and rat and monkey erythrocytes by the method described by Halonen *et al* (31) and heat inactivated at 56 C for 30 min After the erythrocytes were added the plates were incubated at 37°C for 1 hour

Parainfluenza viruses Human type O erythrocytes were used. They were treated as

Rate of the acute respiratory illnesses. ...mong the study groups the rate was calcu...ated monthly and expressed as the ratio of ...ew cases to the number of individuals under ...bservation. Graphs of monthly cumulative ...llness rates are shown in Fig. 1

The respiratory illness rates per person ...ear in the study groups were:

...ursery group:	
infants	6.3
...amily group	
infants	2.5
children 3—6 years	1.5
school-children 7—10 years	0.7
children 11— years	0.3
parents	0.2

... significant differences were observed in the illness experience between the three social groups of the families.

Rate of individual respiratory illnesses The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by infants. Six infants had no symptoms of respiratory illness during their stay in the nursery

In the family group, the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by infants. On the other hand, no acute respiratory illness was reported from 11 infants; 4 of these were newborn babies and one infant was enrolled for onl 6 months Of the children aged —6 years 6 had not experienced any episodes of acut respiratory illness. Among the school-...hildren ..., an l among the oldest children 14 were not reported to have had respiratory symptoms during the study period, and 4 fathers and 33 mothers did not report acute respiratory illnesses. In these data, even the inadequat ly studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory ...ll...ses. Although the total rates of acute respiratory illnesses in the nursery and family infants were not the same, a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower inci...lence was observed during midwinter and in summer

The curve of the cumulative respiratory illness rate in children aged 2—6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a simi...lar pattern of acute respiratory illnesses was seen. The number of acute respiratory ill...nesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows:

Nursery group	
infants	33.3 per cent
Family group	
infants	9.6 per cent
children 2—6 years	5.3 per cent
school-children 7—10 years	1.7 per cent
children 11— years	1.0 per cent
parents	0.6 per cent

Every day on average 5 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average 4 of the children aged —6 years and one of the school-children had respiratory symptoms.

Results

OCCURRENCE OF ACUTE RESPIRATORY ILLNESS

Respiratory illness rate

Criteria for adequately studied illnesses In total, information on 641 acute respiratory illnesses was reported Of these illnesses, 197 occurred in the nursery and 444 among the family group In some cases, the specimen coverage was considered to be inadequate. At least one virus isolation specimen and one blood sample or two blood samples in each respiratory illness were required for adequate coverage.

In the nursery group 7 illnesses remained unstudied by mistake during the observation period and 2 were inadequately studied. In the family group there was not always an opportunity to take the samples. In the infants, 16 of the acute respiratory illnesses were either not studied at all or inadequately studied, in children 2—6 years 10 in school children 5 and in older children and parents 3 of the illnesses. Information about the illnesses inadequately studied is used in the processing of data only if specifically indicated

The total number of adequately studied respiratory illnesses was 598 of these 410 occurred in the family group The number of adequately sampled acute respiratory illnesses in each group was

Nursery group	infants	188
Family group	infants	208
	children 2—6 years	106
	school-children 7—10 years	55
	children 11— years	7
	parents	34

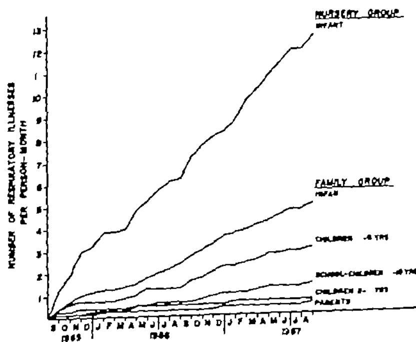


Fig 1 *Cumulative rate of acute respiratory illnesses by month* Each point of the line represents the number of acute respiratory illnesses per person which had occurred between the beginning of the study and the month denoted on the horizontal

Rate of the acute respiratory illnesses. Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig. 1.

The respiratory illness rates per person-year in the study groups were

Nursery group	
infants	6.3
Family group	
infants	2.5
children 2—6 years	1.5
school-children 7—10 years	0.7
children 11— years	0.3
parents	0.2

No significant differences were observed in the illness experience between the three social groups of the families.

Rate of individual respiratory illnesses. The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by 2 infants. Six infants had no symptoms of respiratory illness during their stay in the nursery.

In the family group the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by 2 infants. On the other hand, no acute respiratory illness was reported from 11 infants. 4 of these were newborn babies and one infant was enrolled for only 6 months. Of the children aged 2—6 years 6 had not experienced any episodes of acute respiratory illness. Among the school children 25, and among the oldest children 14 were not reported to have had respiratory symptoms during the study period, and 4 fathers and 33 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory illnesses. Although the total rates of acute respiratory illnesses in the nursery and family infants were not the same, a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer.

The curve of the cumulative respiratory illness rate in children aged 2—6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a similar pattern of acute respiratory illnesses was seen. The number of acute respiratory illnesses among the oldest children and parents was very small.

Weekly prevalance of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows

Nursery group	
infants	33.2 per cent
Family group	
infants	9.6 per cent
children 2—6 years	5.3 per cent
school-children 7—10 years	1.7 per cent
children 11— years	1.0 per cent
parents	0.6 per cent

Every day on average 6 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average 2 of the children aged 2—6 years and one of the school-children had respiratory symptoms.

Results

OCCURRENCE OF ACUTE RESPIRATORY ILLNESS

Respiratory illness rate

Criteria for adequately studied illnesses In total, information on 641 acute respiratory illnesses was reported Of these illnesses, 197 occurred in the nursery and 444 among the family group In some cases, the specimen coverage was considered to be inadequate. At least one virus isolation specimen and one blood sample or two blood samples in each respiratory illness were required for adequate coverage.

In the nursery group 7 illnesses remained unstudied by mistake during the observation period and 2 were inadequately studied In the family group there was not always an opportunity to take the samples. In the infants, 16 of the acute respiratory illnesses were either not studied at all or inadequately studied in children 2—6 years 10 in school children 5 and in older children and parents 3 of the illnesses. Information about the illnesses inadequately studied is used in the processing of data only if specifically indicated.

The total number of adequately studied respiratory illnesses was 598 of these 410 occurred in the family group The number of adequately sampled acute respiratory illnesses in each group was

Nursery group	infants	188
Family group	infants	208
	children 2—6 years	106
	school-children 7—10 years	55
	children 11— years	7
	parents	34

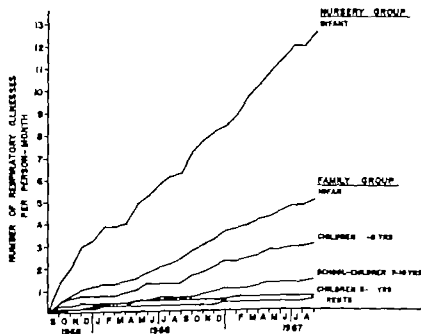


Fig 1. *Cumulative rate of acute respiratory illnesses by month.* Each point on the line represents the number of acute respiratory illnesses per person which had occurred between the beginning of the study and the month denoted on the abscissa.

Rate of the acute respiratory illnesses. Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig. 1

The respiratory illness rates per person-year in the study groups were:

Nursery group	
infants	6.3
Family group	
infants	.5
children ?—6 years	1.5
school-children 7—10 years	0 7
children 11— years	0.3
parents	0._

No significant differences were observed in he illness experience between the three social roups of the families.

Rate of i dividual respiratory illnesses. The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by 2 infants. Six infants had no symptoms of respiratory illness during their stay in the nursery

In the family group the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by infants. On the other hand, no acute respiratory illness was reported from 11 infants 4 of these were newborn babies and one infant was enrolled for only 6 months. Of the children aged ?—6 years 6 had not experienced any episodes of acute respiratory illness. Among the school children .5, and among the oldest children 14 were not reported to have had respiratory symptoms during the study period, and 4_ fathers and 33 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern of acute respiratory ill esses. Although the total rates of acute respiratory illnesses in the nursery and family infants were not the same a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer

The curve of the cumulative respiratory illness rate in children aged ?—6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a simi lar pattern of acute respiratory illnesses was seen. The number of acute respiratory ill nesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows

Nursery group	
infants	33.3 per cent
Family group	
infants	9 6 per cent
children .—6 years	5.3 per cent
school-children 7—10 years	1.7 per cent
children 11— years	1.0 per cent
parents	0.6 per cent

Every day on average 5 infants in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average of the children aged 2—6 years and one of the school-children had respiratory symptoms.

Results

OCCURRENCE OF ACUTE RESPIRATORY ILLNESS

Respiratory illness rate

Criteria for adequately studied illnesses In total information on 641 acute respiratory illnesses was reported. Of these illnesses, 197 occurred in the nursery and 444 among the family group In some cases, the specimen coverage was considered to be inadequate. At least one virus isolation specimen and one blood sample or two blood samples in each respiratory illness were required for adequate coverage.

In the nursery group 7 illnesses remained unstudied by mistake during the observation period and 2 were inadequately studied. In the family group there was not always an opportunity to take the samples. In the infants, 16 of the acute respiratory illnesses were either not studied at all or inadequately studied, in children 2—6 years 10 in school children 5 and in older children and parents 3 of the illnesses. Information about the illnesses inadequately studied is used in the processing of data only if specifically indicated.

The total number of adequately studied respiratory illnesses was 598, of these 410 occurred in the family group The number of adequately sampled acute respiratory illnesses in each group was

Nursery group	infants	188
Family group	infants	208
	children 2—6 years	106
	school-children 7—10 years	55
	children 11— years	7
	parents	34

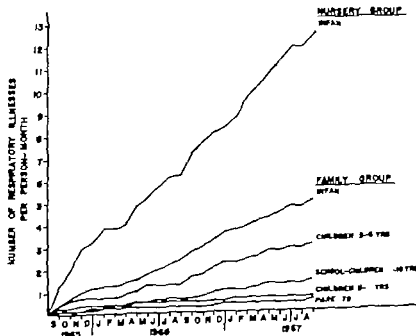


Fig 1 *Cumulative rate of acute respiratory illnesses by month.* Each point on the line represents the number of acute respiratory illnesses per person which had occurred between the beginning of the study and the month denoted on the abscissa.

Rate of the acute respiratory illnesses. Among the study groups the rate was calculated monthly and expressed as the ratio of new cases to the number of individuals under observation. Graphs of monthly cumulative illness rates are shown in Fig 1

The respiratory illness rates per person year in the study groups were

Nursery group	
infants	6.3
Family group	
infants	2.5
children —6 years	1.5
school-children 7—10 years	0.7
children 11 — years	0.3
parents	0._

No significant differences w re observed in the illness experience between the three social groups of the families.

Rate of ind vidual respiratory ill cases. The highest individual illness rate in the nursery group infants adjusted to the length of the observation period was 8.5 illnesses per year experienced by * infants. Six infants had no symptoms f respiratory illness during their stay in the nursery

In the family group the highest individual rate of illness among the infants was 7.8 illnesses per year experienced by * infants. On the other hand, no acute respiratory illness was reported from 11 infants 4 of these were newborn babies and one infant was enrolled for onl 6 months Of the children aged —6 years 6 had not experienced any episodes of acut respiratory illness. Among the school children _5 and among the oldest children 14 re not reported to ha e had respiratory symptoms during the study period, and 4 fathers and 23 mothers did not report acute respiratory illnesses. In these data, even the inadequately studied illnesses were taken into consideration.

Seasonal pattern f acute respiratory illnesses. Although the total *rates of acute* respiratory illnesses in the nursery and family infants were not the same, a general similarity was seen in the seasonal pattern of acute respiratory illnesses. The highest incidence of new acute respiratory illnesses occurred in the fall and spring periods, while a lower incidence was observed during midwinter and in summer

The curve of the cumulative respiratory illness rate in children aged —6 years showed a similar pattern. In the periods with a high frequency of new respiratory illnesses the rate was as high as in the family infants.

In the school-children, a tendency to a simi lar pattern of acute respiratory illnesses was seen. The number of acute respiratory ill nesses among the oldest children and parents was very small.

Weekly prevalence of respiratory symptoms

Prevalence in the study groups. The inadequately studied illnesses were included. Very often the duration of the illness was due to the persistence of nasal discharge only especially in the infants and younger children. The mean weekly prevalence of respiratory symptoms among the groups in the study was as follows.

Nursery group	
infants	33.3 per cent
Family group	
infants	9.6 per cent
children ?—6 years	5.3 per cent
school-children 7—10 years	1 7 per cent
children 11— years	1.0 per cent
parents	0.6 per cent

Every day on average 5 *infants* in the nursery and 4 infants in the family group had respiratory symptoms. Similarly on average of the children aged ?—6 years and one of the school-children had respiratory symptoms.

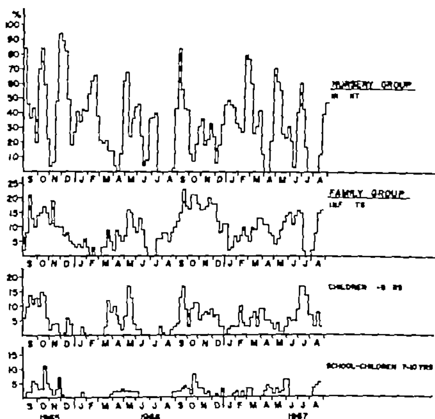


Fig — *Weekly prevalence of re- atory sympt ms.* The mean ek number of persons ill with respir tory symptoms expressed as a pe ce tage of the mean number of indi viduals observed in the week question.

Seasonal prevalence of respiratory symptoms Fig 2 shows the weekly prevalence of respiratory symptoms during the study period in the 4 study groups of infants and children In the nursery group respiratory symptoms occurred in rather clearly distinguishable peaks, indicating new outbreaks of respiratory illness. In the infants of the family group the bar diagram is flattened and shows the seasonal variations rather than weekly outbreaks.

The high prevalence observed in July 1967 in the children aged 2—6 years was due to acute respiratory infections in two families only The few illnesses reported in the school children aged 7—10 years coincided with the highest peaks of prevalence among the family infants. In the oldest children the highest prevalence of respiratory symptoms was 12 per cent in April 1966 Otherwise only one of these children had respiratory symptoms at any time The highest prevalence observed in parents was 4 per cent in November 1965 and April 1967 The respiratory illnesses of the parents were sporadic but in only 3 months were no symptoms of respiratory illness reported among the parents.

VIRUS ISOLATIONS AND SEROLOGIC TESTS

An acute respiratory illness was considered to have a diagnosed virus etiology according to the following principles.

Only virus isolations followed by a 4-fold or greater antibody rise relevant to the isolation were considered acceptable as evidence of the etiology Some exceptions to this will be indicated in the sections concerned.

A 4-fold or greater rise in antibody titer in CF HI and/or neutralization tests during a period not longer than 6 weeks was also considered acceptable as evidence of the etiology

In Table 4 the etiology of the acute respiratory illnesses in both study groups is summarized

Table 4 *Virus etiology in the 598 acute respiratory illnesses*

Illness group	Nursery group		Family group									
	Infants (188 illnesses)		Infants (208 illnesses)		Children 3—6 yrs (106 illnesses)		School-children 7—10 yrs (55 illnesses)		Children 11— yrs (7 illnesses)		Parents (34 illnesses)	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
RS	14	7.4	25	12.0	15	14.2	6	10.9	—	—	—	—
Parainfluenza	7	3.7	23	11.1	7	6.6	5	9.1	—	—	1	2.9
Influenza A2	—	—	4	1.9	5	4.7	4	7.3	—	—	2	5.9
Adeno	35	18.6	26	12.5	18	17.0	5	9.1	—	—	3	8.8
Coxsackie B	2	1.1	3	1.4	4	3.8	—	—	1	14.3	—	—
ECHO 9	—	—	2	1.0	1	0.9	—	—	—	—	1	2.9
Herpes simplex	—	—	1	0.5	—	—	—	—	—	—	—	—
Total positive rate	58/188	30.8	84/208	40.4	50/106	47.2	20/55	36.4	1/7	14.3	7/34	20.5

The total rate of detected virus infections in the acute respiratory illnesses of the infants in the family group was higher than in the infants of the nursery group ($p < 0.05$ t test). A greater variety of viruses were found in the infants of the family group. No significant difference in the rate of detected virus infections was observed between the three social groups of families.

The distribution of the acute respiratory illnesses with detected virus etiology was different among the infants in the nursery

Table 5. *Virus etiology of the 188 acute respiratory illnesses in the infants of the nursery group*

Virus	Virus isolation		Significant antibody rise	Total number of infections
	Pharyngeal swab	Rectal swab		
RS	14	—	12	14
Parainfluenza				
type 3	1	—	6	7
Adeno				
type 1	5	1	6	8
type 2	1(+2)	1(+2)	3(+2)	3(+2)
type 3	9(+2)	3(+1)	11(+1)	11(+1)
type 6	1	—	3	3
type 7	—	—	3	3
untyped	—	1	7 (+1)	7(+1)
Coxsackie B				
type 5	2	—	2	2
Total	33(+4)	8(+3)	53(+4)	58(+4)

Figures in parentheses indicate concurrent infection with RS virus, which was considered to be the main etiologic agent.
** Antibody rise in CF test.

and family groups ($p = 0.001$ chi-square test) The differences between the infants and the children aged 2—6 years in the family group were not statistically significant

Infants of the nursery group The results of relevant virus isolations and antibody rises in the 188 acute respiratory illnesses in the infants of the nursery group are given in Table 5

Of the original 57 pharyngeal and 16 rectal isolates, only 33 from pharyngeal and 2 from rectal swabs were considered to be etiologic agents (18 6 per cent positive) Fourteen adenovirus strains were detected in both pharyngeal and rectal swabs on the same occasion and treated as a single isolatio 8 cases of virus isolation there was pos tive evidence that the Coxsackie B ty and adenoviruses isolated were not etiol agents in the current illnesses because virus had been isolated earlier or a signifi serologic rise to the type had occurred earl Adenoviruses types 1 2 and 5 not foll by an antibody rise were isolated from infants in 3 cases RS or parainfluenza vi infections were simultaneously detected C third of these adenovirus isolations sporadic.

The virus isolations and serologic res of the RS virus outbreak have been describ

Table 6 *Virus etiology of the 208 acute respiratory illnesses in the infants of the fam group*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	13	24	[illegible]
Parainfluenza:			
type 1	4	0	6
type	1	3	3
type 3	4	8	9
untyped	3	5	5
Influenza A2	3	4	4
Adeno:			
type 1	5	0	6
type 2	2(+1)	3(+)	3(+2)
type 3	2	3	3
type 5		3(+1)	5(+1)
type 6	1	—	1
type 7	1	4(+1)	4(+1)
untyped	—	5(+1)	4(+1
Coxsackie B:			
type 2	1	1	1
type 5	2	2	2
ECHO 9	1	3	2
Herpes simplex	1(+1)	1(+2)	1(+3)
Total	40(+2)	82(+7)	84(+7)

Figures in parentheses indicate double infections with RS or parainfluenza viruses, which were considered to be the main etiologic ag nts.
The other a double infectio with adeno irus type 7

in detail elsewhere (29). One isolation of parainfluenza virus type 3 was considered significant even though the convalescent phase serum specimen was not available because the isolation was obtained during a parainfluenza virus type 3 outbreak.

Following the procedure of Berglund (7) the RS virus was isolated from the middle ear exudates of 5 infants with otitis media during the RS virus outbreaks. These studies have been described in detail earlier (29).

Infants of the family group. The results of relevant virus isolations and antibody rises are shown in Table 6. From the 208 acute respiratory illnesses 55 virus strains were isolated, but the number of significant isolations was 46 (22.0 per cent positive).

One RS virus isolation without antibody rise was considered adequate for identification because the convalescent phase serum specimen was taken relatively soon after the onset of the illness. This was also the case in one isolation of parainfluenza type 3. The isolation of adenovirus type 6 shown in Table 5 was only confirmed by a significant rise in the CF test. Six sporadic isolations of adenoviruses and one of herpes simplex virus were not followed by an antibody rise.

Children of the family group aged 2—6 years. The results of the relevant virus isolations and antibody rises are given in Table 7.

The 106 acute respiratory illnesses of this group yielded 30 virus isolates, 26 of which were considered significant (24.6 per cent positive).

Table 7. *Virus etiology of the 106 acute respiratory ill cases in the children of the family group aged 2—6 years*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	0	13	13
Parainfluenza			
type 3	—	4	4
untyped	1**	3**	3
Influenza A2	4	5	5
Adeno			
type 1	2	3	3
type 2	1	4	4
type 3	2	2	2
type 5	0	3	3
type 6	1	1	1
type 7	2	3	3
Coxsackie B			
type 2	3	4	4
ECHO 9	1	1	1
Herpes simplex	—	—(+1)	—(+1)
Total	26	30(+1)	30(+1)

Figure in parentheses indicates double infection with adenovirus type 6.
The isolate, positive in hemadsorption had low hemagglutinating activity and could not be passaged; the paired sera yielded equal rises to parainfluenza types 1 and 3 in CF and HI tests.

and family groups ($p = 0.001$ chi-square test) The differences between the infants and the children aged 2—6 years in the family group were not statistically significant

Infants of the nursery group The results of relevant virus isolations and antibody rises in the 188 acute respiratory illnesses in the infants of the nursery group are given in Table 5

Of the original 57 pharyngeal and 16 rectal isolates, only 33 from pharyngeal and 2 from rectal swabs were considered to be etiologic agents (18.6 per cent positive) Fourteen adenovirus strains were detected in both pharyngeal and rectal swabs on the same occasion and treated as a single isolation 8 cases of virus isolation there was presump tive evidence that the Coxsackie B type and adenoviruses isolated were not etiologic agents in the current illnesses, because th virus had been isolated earlier or a significan serologic rise to the type had occurred earlier Adenoviruses types 1 2 and 5 not followe by an antibody rise were isolated from 1 infants in 3 cases RS or parainfluenza vir infections were simultaneously detected On third of these adenovirus isolations wer sporadic.

The virus isolations and serologic results of the RS virus outbreak have been described

Table 6 *Virus etiology of the 208 acute respiratory illnesses in the infants of the family group*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	T tal number of infections
RS	13	4	23
Parainfluenza:			
type 1	4	6	6
type	1	3	3
type 3	4	8	9
untyped	3	5	5
Influenza A3	3	4	4
Adeno:			
type 1	5	6	6
type 2	3(+1)	3(+)	3(+)
type 3	3	3	3
type 5	2	3(+1)	5(+1)
type 6	1	—	1
type 7	1	4(+1)	4(+1)
untyped	—	3(+1)	4(+1)
Coxsackie B			
type	1	1	1
type 3		2	
ECHO 9	1	3	3
Herpes simplex	1(+1)	1(+2)	1(+)
Total	46(+3)	82(+7)	84(+7)

Figures in para theses indicate double infections with RS or parainfluenza iruses, which were considered to be the main etiologic gents.
The other a double infection with adenovirus type 7

viruses and 3 of herpes simplex virus were not followed by antibody responses.

In the group of oldest family children only one significant serologic rise to Coxsackie B type was observed and no viruses were isolated.

Parents of the family group The results of the relevant virus isolations and antibody rises are shown in Table 9 From the observed 34 cases of illness 5 viruses were isolated. One adenovirus isolation was not followed by an antibody rise.

In the family group the total number of acute respiratory illnesses with identified viral etiology was 162 in the 410 illnesses studied (39.5 per cent positive) The number of significant antibody rises was 169 (38.8 per cent positive) and the number of etiologically relevant virus isolations 85 (20 7 per cent) In 11 cases a double infection was detected.

IDENTIFIED VIRUS INFECTIONS

In Fig 3 the monthly frequency of acute respiratory illnesses with identified viral etiology with respect to the total monthly number of illnesses observed is presented. In almost every month some acute respiratory illnesses were diagnosed virologically but only on a few occasions was a high percentage of diagnosed illnesses recorded.

RS virus infections

As already stated, all evidence of RS virus infection was considered to be etiologically significant. No infections with RS virus were observed among oldest children and parents.

In Fig 4 the prevalence of RS infection is shown. In the families the RS infections occurred in two outbreaks, in the first 26 per cent of the infants contracted it, and in the second the attack rate was 25 per cent in both infants and children aged —6 years.

In the nursery group only one outbreak of RS virus infections occurred, when all the infants contracted it. This outbreak has been described in detail in connection with the studies of RS virus in the *middle ear exudates*

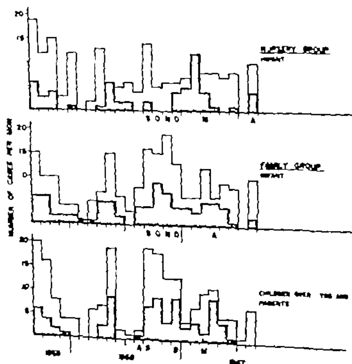


Fig 3. The number of acute respiratory illnesses with identified viral etiology (shaded) and the total monthly number of illnesses studied

Table 8 *Virus etiology of the 55 acute respiratory illnesses in the school-children of the family group aged 7—10 years*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
RS	—	0	0
Parainfluenza			
type 2	3	2	
type 3	1		
untyped	—	1	1
Influenza A2		3	4
Adeno:			
type 1	1	1(+1)	1(+1)
type 3	2	3	3
type 7	1	1	1
Herpes simplex	—	—(+1)	—(+1)
Total	9	19(+2)	20(+2)

Figures in parentheses indicate double infections with influenza A2 and RS viruses, which were considered to be the main etiologic agents.
Equal rises in parainfluenza types 1 and 3 antibodies in CF and HI tests.

Two isolations of adenoviruses and two of herpes simplex virus were not followed by an antibody rise.

School-children of the family group. The results of the relevant virus isolations and antibody rises in the school-children aged 7—10 years are shown in Table 8.

From the 55 cases of acute respiratory illness reported 14 virus isolates were obtained. One influenza A2 virus isolation without antibody rise was considered to be significant because the CF and HI antibody titers were already very high in the acute phase specimen. Two isolations of adeno-

Table 9 *Virus etiology of the 31 acute respiratory illnesses in the parents of the family group*

Virus	Virus isolation Pharyngeal swab	Significant antibody rise	Total number of infections
Parainfluenza			
type 3	—	1	1
Influenza A2	1		2
Adeno			
type 1	3	3	3
ECHO 9	1	1	1
Herpes simplex	—	—(+1)	—(+1)
Total	4	7(+1)	7(+1)

Figure in parentheses indicates a double infection with adenovirus type 1

infections occurred and only one infection with parainfluenza virus type 3 was observed in the parents.

In Fig. 5 the parainfluenza virus infections of the infants and children are shown. At the time when the parainfluenza virus type 3 outbreak occurred in the nursery when 50 per cent of the infants contracted it, the same type was prevalent among the family infants and children, with an attack rate of approximately 70 per cent. Sporadic cases of parainfluenza virus infection occurred in the family group in the fall and spring seasons. In March and May 1967 several cases of illness due to parainfluenza virus types 1 and were observed in the infants of the family group.

In the nursery the infection rate of parainfluenza virus was 0.23 per person year. In the family infants the infection rate was 0.26 per person-year the same as observed among the nursery infants. The rates of parainfluenza virus infection were 0.08 per person-year in children aged 2—6 years and 0.03 in school children of the family group.

Influenza A2 virus infections

No cases of influenza A2 infection were seen in the nursery. In the family group, one sporadic infection with influenza A2 was observed in September 1966, but in April—May 1967 family outbreaks occurred. The infection spread within 4 families (10.5 per cent of the families under observation) and was experienced by 14 individuals (Fig. 6).

Adenovirus infections

Infection rate. Infections indicated by the first isolation of an adenovirus without detectable antibody response were also included. In the nursery group 51 adenovirus infections occurred, in the infants of the family group 31 in the children aged 2—6 years 19 in school-children and parents 10 infections.

Fig. 7 shows the cumulative adenovirus infection rates and the appropriate cases in the study groups.

The prevelence of adenovirus infections was highest in the infants of the nursery group 1.7 per person year. In the infants of the family group the rate was 0.4 in children aged —6 years 0.3 and in school-children only 0.1 per person year. The adenovirus infection rate in the nursery was 4-fold that observed in the infants of the family group.

Adenovirus types. The commonest types were 1 ? and 5. The distribution of adenovirus types in the illnesses with adenovirus etiology in the younger children is shown in Tables 5 6 and 7. There are no significant differences between the groups.

In Fig. 8 the occurrence of the adenovirus types 1 and 5 among the infants is shown. Adenovirus type 1 reached an infection rate of 0.5 per person year in the nursery group while it was only 0.08 per person year in the infants of the family group. Thus, compared to the rate observed in the infants of the family group, the rate in the nursery was 3-fold. The infections with type 1 were sporadic.

In the infants of the nursery group, the infection rate of adenovirus type 2 was 0.5

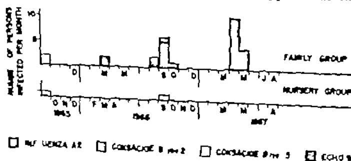


Fig. 6. *Influenza A2* and entero-virus infections

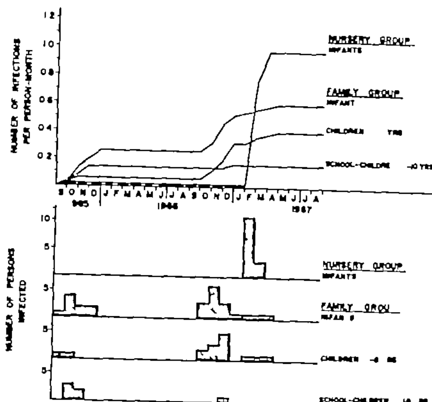


Fig 4 *RS rus f ctions.* Cumulati e rat f RS infections and the cases observed

of infants with otitis media published elsewhere (29)

In the nursery group infants the RS virus infection rate was 0.5 per person year In the infants of the family group the rate was 0.3 per person year In the nursery infants the rate exceeded that found in the family infants by 1 7 fold. In the family group children aged 2—6 years had an RS infection rate of 0 2 per person year and the school children a rate of 0 1 per person year The double infections of RS virus and some other virus were described in a previous section.

Parainfluenza virus infections

All the parainfluenza virus infections detected were considered to be etiologically significant In the oldest children no parainfluenza virus

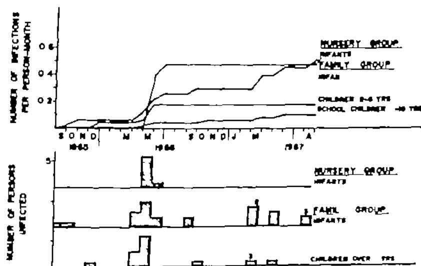


Fig 5. *Par flu. n s fec t* as Cumulati rat of parainflue za virus infectio nd the cases ol served. The umbers in the lo dia gram indicat the type f the para influenza irus.

infections occurred and only one infection with parainfluenza virus type 3 was observed in the parents.

In Fig. 5 the parainfluenza virus infections of the infants and children are shown. At the time when the parainfluenza virus type 3 outbreak occurred in the nursery when 50 per cent of the infants contracted it, the same type was prevalent among the family infants and children, with an attack rate of approximately 20 per cent. Sporadic cases of parainfluenza virus infection occurred in the family group in the fall and spring seasons. In March and May 1967 several cases of illness due to parainfluenza virus types 1 and 2 were observed in the infants of the family group.

In the nursery the infection rate of parainfluenza virus was 0.23 per person year. In the family infants the infection rate was 0.26 per person year, the same as observed among the nursery infants. The rates of parainfluenza virus infection were 0.08 per person-year in children aged —6 years and 0.05 in school children of the family group.

Influenza A2 virus infections

No cases of influenza A2 infection were seen in the nursery. In the family group one sporadic infection with influenza A2 was observed in September 1966, but in April—May 1967 family outbreaks occurred. The infection spread within 4 families (10.5 per cent of the families under observation) and was experienced by 14 individuals (Fig. 6).

Adenovirus infections

Infection rate. Infections indicated by the first isolation of an adenovirus without detectable antibody response were also included. In the nursery group 51 adenovirus infections occurred, in the infants of the family group 31, in the children aged —6 years 19, in school-children and parents 10 infections.

Fig. 7 shows the cumulative adenovirus infection rates and the appropriate cases in the study groups.

The prevalence of adenovirus infections was highest in the infants of the nursery group 1.7 per person year. In the infants of the family group the rate was 0.4, in children aged 2—6 years 0.3 and in school-children only 0.1 per person year. The adenovirus infection rate in the nursery was 4-fold that observed in the infants of the family group.

Adenovirus types. The commonest types were 1, 2 and 5. The distribution of adenovirus types in the illnesses with adenovirus etiology in the younger children is shown in Tables 5, 6 and 7. There are no significant differences between the groups.

In Fig. 8 the occurrence of the adenovirus types 1, 2 and 5 among the infants is shown. Adenovirus type 1 reached an infection rate of 0.23 per person year in the nursery group while it was only 0.06 per person-year in the infants of the family group. Thus, compared to the rate observed in the infants of the family group, the rate in the nursery was 3-fold. The infections with type 1 were sporadic.

In the infants of the nursery group, the infection rate of adenovirus type 2 was 0.5

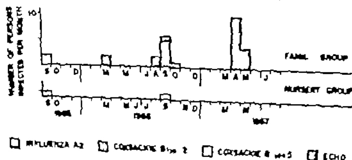


Fig. 6. Influenza A2 and ... virus infections

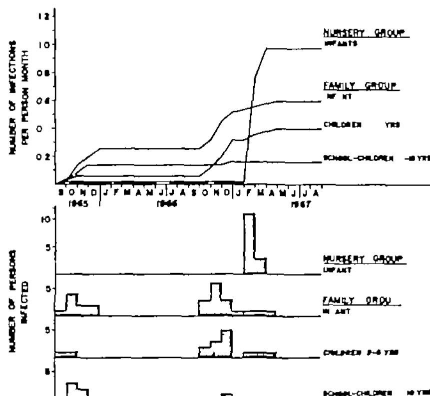


Fig 4 *RS virus infections.* Cumulative rate of RS infections and the cases observed.

of infants with otitis media published elsewhere (29)

In the nursery group infants the RS virus infection rate was 0.5 per person year In the infants of the family group the rate was 0.3 per person year In the nursery infants the rate exceeded that found in the family infants by 1 7 fold. In the family group children aged 2—6 years had an RS infection rate of 0 2 per person year and the school children a rate of 0 1 per person year The double infections of RS virus and some other virus were described in a previous section.

Parainfluenza virus infections

All the parainfluenza virus infections detected were considered to be etiologically significant. In the oldest children no parainfluenza virus

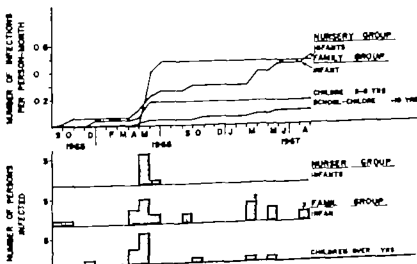


Fig 5. *Parai fluenza irus fco t ns.* Cumulati rate of parainflue za irus infections and the cases observed. The umbers in the bar dia gram indicat the type f the para influenza irus.

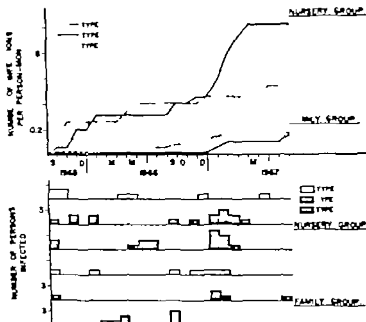


Fig 8 *Infections with adenovirus types 1 2 and 5 among the fonts.* Cumulative infection rates and the cases observed in the infants f the nursery and family groups.

(Fig. 6) In March 1966 a mother and daughter and in August 1966 twin brothers contracted this infection

Herpes simplex infections

In one infant herpes simplex virus was the only etiologic agent detected All the other infections with herpes simplex were observed in connection with infections with other viruses. All the cases were sporadic.

Comparison of outbreaks with identified virus etiology and outbreaks of unknown etiology

The outbreaks were presented in Fig. ..

The etiologic agents in the observed outbreaks of acute respiratory illness were the following:

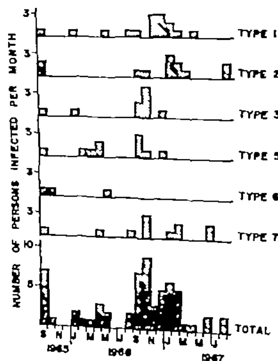


Fig. 9 Adenovirus types 1—7 associated with respiratory illnesses of adenovirus etiology the f mily group

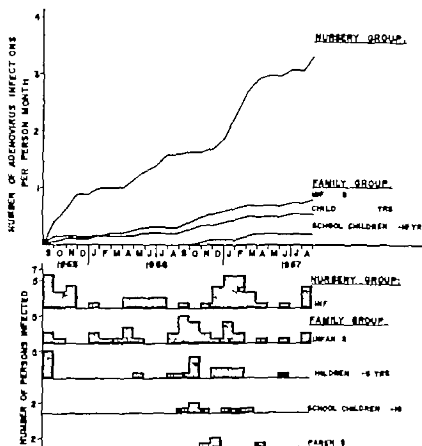


Fig 7 *Adenovirus infections.* Cumulative rate of adenovirus infections and the cases observed.

per person year In the infants of the family group the rate was only 1/6th, 0 08 per person year

The infection rate of type 5 was as high as the rate of type 2 in the infants of the nursery group 0.5 per person year The prevalence of type 5 among the family infants was of a low order 0 08 per person year

The adenovirus types 2 and 5 each comprised one-third of the adenovirus infections in the nursery but among the infants of the family group types 1 2 and 5 were equally frequent.

In August 1967 4 cases of CF rises to adenovirus antibodies were observed in the nursery one of these with isolation of an adenovirus. These could not be proved to belong to the types 1—7 tested

In Fig 9 the illnesses with adenovirus etiology in the families are shown Summarizing among the families types 1 2, 3 and 5 occurred in small outbreaks, type 7 sporadically and only 3 cases of type 6 infection were detected.

Enterovirus infections

An outbreak of respiratory illness associated with Coxsackie B type 2 infection was observed in the families in September—October 1966 (Fig 6) The cases observed were from 4 families. In addition 2 children in a fifth family showed high antibody titers to this virus, but no rise was demonstrated

In September 1967 a few Coxsackie B type 5 infections were observed simultaneously in the infants of the nursery and family groups (Fig 6) One sporadic case of Coxsackie B type 5 infection was observed in the nursery in September 1966

In the family group 4 infections with ECHO 9 virus were detected in two families

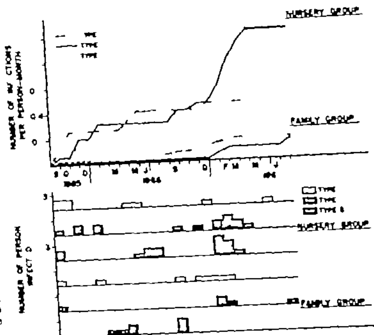


Fig. 8. Infections with adenovirus types 1, 3 and 5 among the infants. Cumulative infection rates and the cases observed in the infants of the nursery and family groups.

(Fig. 6) In March 1966 a mother and daughter and in August 1966 twin brothers contracted this infection.

Herpes simplex infections

In one infant herpes simplex virus was the only etiologic agent detected. All the other infections with herpes simplex were observed in connection with infections with other viruses. All the cases were sporadic.

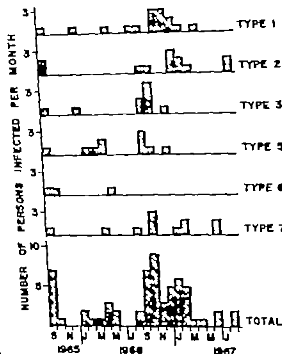


Fig. 9. Adenovirus types 1—7 associated with respiratory illness of adenovirus etiology in the family group

Comparison of outbreaks with identified virus etiology and outbreaks of unknown etiology

The outbreaks were presented in Fig. 4.

The etiologic agents in the observed outbreaks of acute respiratory illness were the following:

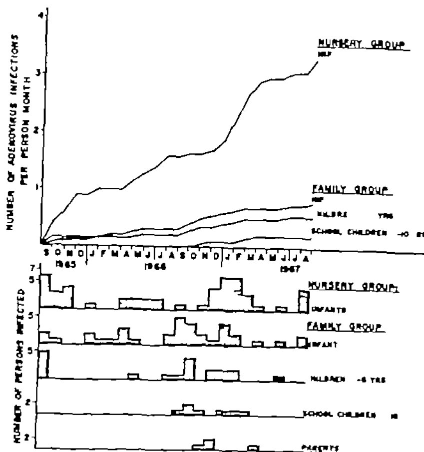


Fig 7 *Adenovirus infections.* Cumulative rate of adenovirus infection and the cases observed.

per person year In the infants of the family group the rate was only 1/6th, 0 08 per person year

The infection rate of type 5 was as high as the rate of type 2 in the infants of the nursery group 0.5 per person year The prevalence of type 5 among the family infants was of a low order 0 08 per person year

The adenovirus types 2 and 5 each comprised one-third of the adenovirus infections in the nursery but among the infants of the family group types 1 2 and 5 were equally frequent

In August 1967 4 cases of CF rises to adenovirus antibodies were observed in the nursery one of these with isolation of an adenovirus. These could not be proved to belong to the types 1—7 tested.

In Fig 9 the illnesses with adenovirus etiology in the families are shown Summarizing among the families types 1 2, 3 and 5 occurred in small outbreaks, type 7 sporadically and only 3 cases of type 6 infection were detected.

Enterovirus infections

An outbreak of respiratory illness associated with Coxsackie B type ₋ infection was observed in the families in September—October 1966 (Fig 6) The cases observed were from 4 families. In addition 2 children in a fifth family showed high antibody titers to this virus, but no rise was demonstrated

In September 1965 a few Coxsackie B type 5 infections were observed simultaneously in the infants of the nursery and family groups (Fig 6) One sporadic case of Coxsackie B type 5 infection was observed in the nursery in September 1966

In the family group 4 infections with ECHO 9 virus were detected in two families

Other children of the family group

Children aged —6 years

Outbreaks of respiratory illness		Etiologic agents
1965	September	adenoviruses
	October	RS virus, unknown
1966	March—April	unknown
	May	parainfluenza virus type 3
	September	Coxsackie B type —, unknown
	October	adenoviruses, RS virus
	November	RS virus
	December	RS virus
1967	April	influenza A— virus
	June—July	unknown

In 2 of the 10 outbreaks the etiology was wholly obscure, 4 were associated with infection by a single virus (Figures 4—6) and the others were due to infections with several viruses.

In the school-children aged 7—10 three outbreaks of illness were observed the first was associated with parainfluenza virus type 3 infection. In the other outbreaks the etiologic agents were not identified.

In the infants of the nursery group and of the family group the outbreaks of respiratory illnesses with specific virus etiology corresponded only in September 1965 (adenoviruses, Coxsackie B type 5) and May 1966 (parainfluenza virus type 3). In five simultaneously occurring outbreaks the etiology remained totally or partially obscure.

CLINICAL OBSERVATIONS

Clinical diagnosis of acute respiratory illness

Distribution of ill cases to upper and lower respiratory tract infections. The term upper respiratory illness (URI) includes the illnesses with symptoms from nose to trachea. Similarly lower respiratory illness (LRI) includes all illnesses with involvement of the lower respiratory tract.

In Table 10 the clinical diagnoses in the acute respiratory illnesses with detected virus etiology and with unknown etiology are shown. In addition, in the nursery infants two cases of URI were associated with a Coxsackie B type 5 infection. In the family infants 7 cases of URI were associated with influenza A2, Coxsackie B type 5, ECHO virus type 9 and herpes simplex virus infections, and in three cases of bronchitis influenza A2, Coxsackie B virus type 2 and 5 were the etiologic agents.

The ratios of URI to LRI were compared by the chi-square test. Among the infants of the nursery group there was a highly significant difference between the ratios for the illnesses with detected virus etiology and those of unknown etiology. Among the infants of the family group there was no such difference. Between the infants of the nursery and family groups the ratios differed significantly among the illnesses of unknown etiology but not among the illnesses with detected virus etiology.

Even the illnesses with detected virus etiology were more often mild in the older children.

Infants of the nursery group

Outbreaks of respiratory illness		Etiologic agents
1965	September	adenovirus types 1 5 Coxsackie B type 5 unknown
	October	adenovirus types 1 6 unknown
	November	adenovirus types 2, 6 unknown
1966	January—February	unknown
	April	unknown
	May	parainfluenza virus type 3
	June—July	adenovirus type 5 unknown
	August—September	unknown
	October—November	unknown
	December	adenovirus type 7
1967	January	adenovirus types 5 2
	February—March	RS virus
	April—May	unknown
	June	unknown
	August	untyped adenovirus, unknown

Among the 15 major outbreaks of acute respiratory illness, the etiology was not established in 6 and was only partially established in 5 4 outbreaks were associa with parainfluenza virus type 3 adenoviru or RS virus (Figures 5 7 8 and 4)

Infants of the family group

Outbreaks of respiratory illness		Etiologic agents
1965	September	adenoviruses, Coxsackie B type 5 RS virus
	October	RS virus
	November	unknown
1966	April	parainfluenza virus type 3 adenovirus type 5
	May	parainfluenza virus type 3 unknown
	June	unknown
	July—August	unknown
	September	adenoviruses, parainfluenza virus type 1 unknown
	October	adenoviruses, RS virus, Coxsackie B type 2
	November	RS virus, unknown
	December	RS virus, unknown
1967	March	parainfluenza virus type 1 2
	April	influenza virus A2
	May	parainfluenza virus type 1
	June—July	unknown
	August	unknown parainfluenza virus type 3

In 4 of the 16 outbreaks the etiology remained wholly obscure and in 5 it was only partially clarified. In 4 of the outbreaks several viruses were together responsible for the outbreak. Three outbreaks were associate with RS, parainfluenza and influenza viruses (Figures 4—6)

Other children of the family group

Children aged –6 years

Outbreaks of respiratory illness		Etiologic agents
1965	September	adenoviruses
	October	RS virus, unknown
1966	March—April	unknown
	May	parainfluenza virus type 3
	September	Coxsackie B type –, unknown
	October	adenoviruses, RS virus
	November	RS virus
	December	RS virus
1967	April	influenza A– virus
	June—July	unknown

In of the 10 outbreaks the etiology was wholly obscure, 4 were associated with infection by a single virus (Figures 4—6) and the others were due to infections with several viruses.

In the school-children aged 7—10 three outbreaks of illness were observed the first was associated with parainfluenza virus type 3 infection. In the other outbreaks the etiologic agents were not identified.

In the infants f the nursery group and of the family group the outbreaks of respiratory illnesses with specific virus etiology corresponded onl in September 1965 (adenoviruses, Coxsackie B type 5) and May 1966 (parainfluenza virus type 3) In five simultaneously occurring outbreaks the etiology remained totally or partially obscure

CLINICAL OBSERVATIONS

Clinical diagnosis of acute respiratory illness

Distribution of illnesses to upper a d lower respiratory tract i fections. The term upper respiratory illness (URI) includes the illnesses with symptoms from nose to trachea. Similarly low r respiratory illness (LRI) includes all illnesses with involvement of the lower respiratory tract.

In Table 10 the clinical diagnoses in the acute respiratory illnesses with detected virus etiology and with unknown etiology are shown. In addition in the nursery infants two cases of URI were associated with a Coxsackie B type 5 infection In the family infants 7 cases of URI were associated with influenza A–, Coxsackie B type 5, ECHO virus type 9 and herpes simplex virus infections, and in three cases of bronchitis influenza A–, Coxsackie B virus type and 5 were the etiologic agents.

The ratios of URI to LRI were compared by the chi-square test. Among the infants of the nursery group there was a highly significant difference between the ratios for the illnesses with detected virus etiology and those of unknown etiology Among the infants of the family group there was no such difference. Between the infants of the nursery and family groups the ratios differed significantly among the illnesses of unknown etiology but no among the illnesses with detected virus etiology

Even the illnesses with detected virus etiology were more often mild in the older children.

Tablo 10 *Clinical diagnosis of the acute respiratory illnesses*

Illnesses	Illnesses with detected virus etiology												Illnesses of unknown etiology			
	Nursery group					Family group							Nursery group	Family group		
	Infant					Infant					Children —6 yrs	Other members	Infant	Infants	Children —6 yrs	Other members
	RS	*Para influenza*	*Adeno*	*Other*	Total	*RS*	*Para influenza*	*Adeno*	*Other*	Total	Total	Total				
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
URI		4	30	2	38	13	1	22	7	64	41	4	119	91	53	64
Croup	—	—	—	—	—		7		—	11	5		—	6	—	4
Bronchitis	7	3	5	—	15	0	4		3	15	4		10	[illegible]	3	—
Bronchiolitis	3	—	—	—	3		—	—	—		—	—	—	—	—	—
Pneumonia		—	—	—			—	—	—		—	—	1	1	—	—
Total number of illnesses	14	7	33		58	[illegible]	23	0	10	84	50	[illegible]	130	1 4	56	68

In the nursery group the differences in proportions of URI and bronchitis between the RS, parainfluenza and adenovirus groups were very highly significant (chi-square test) In the family infants among the RS, para influenza and adenovirus infections the difference was less significant ($p < 0.05$) When the distributions of diagnosis in each virus group were compared with the corresponding distribution in the other infant group no significant differences could be observed.

Clinical conditions requiring hospitalization. During the RS virus outbreak in the nursery 4 infants were sent to hospitals with clinical diagnoses of bronchitis, bronchiolitis and broncho-pneumonia (29) In addition, one baby with pneumonia of unknown etiology was hospitalized in December 1965

One infant in the family group was twice sent to hospital with pneumonia, which on one of these occasions was associated with RS virus infection. No other admissions because of respiratory illnesses occurred during the study period.

Signs and symptoms

The most frequent signs and symptoms in the acute respiratory illnesses observed are shown in Table 11 The distributions in the frequencies of the signs and symptoms were compared by the chi-square test Among the infants of the nursery group the difference in the frequencies between illnesses with detected virus and unknown etiology was highly significant, but among the other groups the differences were not significant Among the illnesses with detected virus etiology between the infants of the nursery and family groups the difference in the frequencies was significant but it was highly significant among the illnesses with unknown etiology

Sore throat was more common in the older members of the family group than in the

Table 11. Commonly observed signs and symptoms in respiratory illnesses

Signs and symptoms	Illnesses with detected virus etiology				Illnesses of unknown etiology			
	Nursery group	Family group			Nursery group	Family group		
	Infants (58 illnesses)	Infants (84 illnesses)	Children 2—6 yrs (90 illnesses)	Other members (28 illnesses)	Infants (120 illnesses)	Infants (1 4 illnesses)	Children 2—6 yrs (34 illnesses)	Other members (66 illnesses)
	%	%	%	%	%	%	%	%
Nasal discharge	100	98	100	100	100	100	93	97
Cough	66	69	81	61	59	68	89	57
Sore throat	—	1	8	26	—	1	7	53
Injected pharynx	84	63	94	64	73	86	60	90
Hoarseness	3	50	8	11	1	10	12	5
Rhonchi	29	19	8	7	8	22	7	—
Cervical lymphadenopathy	—	38	4	29	7	29	37	32
Otitis media	26	51	6	—	6	19	4	—
Gastrointestinal symptoms	3	8	14	7	7	10	4	0

children aged 2—6 years (in illnesses with *detected virus etiology* $p < 0.01$, in illnesses of unknown etiology $p < 0.001$ t-test). Rhonchi were observed more often in the nursery group infants in illnesses with detected virus etiology ($p < 0.01$ t-test). The same significant difference was observed in the occurrence of otitis media in illnesses with detected virus etiology and of unknown etiology among the infants of the nursery group.

In addition, râles were observed in ? infants in the nursery, one of these had an RS virus infection. Expiratory wheezing was present in 5 infants with RS virus infection who also had general symptoms of the bronchiolitis syndrome (29). Conjunctivitis was observed in only one infant with an adenovirus infection and in two with illness of unknown etiology.

In the infants of the family group lymphadenitis was observed in 11 out of 23 parainfluenza virus infections and 9 out of ?6 adenovirus infections, and otitis media in 9 out of 25 RS and 6 out of 23 parainfluenza virus infection. Signs of bronchiolitis were observed in 5 infants with RS virus infection and one with parainfluenza virus infection. Râles were heard in two infants with RS virus infection and in one with illness of unknown etiology. Conjunctivitis was observed in 5 infants with adenovirus, RS and parainfluenza virus infections and in 6 infants with illness of unknown etiology.

Fever

Prevalence of fever. The results of the temperature readings were divided into three classes according to the highest temperature observed.

No fever	temperature ≦ 37.5 C
Low fever	temperature = 37.6 —38.5 C
High fever	temperature ≧ 38.6° C

Table 10 *Clinical diagnosis of the acute respiratory illnesses*

Illnesses	Illnesses with detected virus etiology												Ill cases of unknown etiology			
	Nursery group					Family group							Nursery group	Family group		
	Infants					Infants					Children 2—6 yrs	Other members	Infants	Infants	Children —6 yrs	Other members
	RS	*Para influenza*	*Adeno*	*Other*	Total	*RS*	*Para fluenza*	*Adeno*	*Other*	Total	Total	Total				
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
URI	2	4	30	2	38	13	12	23	7	54	41	24	119	91	53	64
Croup	—	—	—	—	—		7		—	11	5	2	—	6	—	4
Bronchitis	7	3	5	—	15	6	4	2	3	15	4	2	10	20	3	—
Bronchiolitis	3	—	—	—	3		—	—	—	2	—	—	—	—	—	—
Pneumonia		—	—	—	2		—	—	—	2	—	—	1	1	—	—
Total number of illnesses	14	7	35	2	58	[illegible]	23	[illegible]	10	84	50	28	130	124	[illegible]	68

In the nursery group the differences in proportions of URI and bronchitis between the RS parainfluenza and adenovirus groups were very highly significant (chi-square test) In the family infants among the RS, para influenza and adenovirus infections the difference was less significant ($p < 0.05$) When the distributions of diagnosis in each virus group were compared with the corresponding distribution in the other infant group no significant differences could be observed.

Clinical conditions requiring hospitalization. During the RS virus outbreak in the nursery 4 infants were sent to hospitals with clinical diagnoses of bronchitis, bronchiolitis and broncho-pneumonia (29) In addition one baby with pneumonia of unknown etiology was hospitalized in December 1965

One infant in the family group was twice sent to hospital with pneumonia, which on one of these occasions was associated with RS virus infection No other admissions because of respiratory illnesses occurred during the study period

Signs and symptoms

The most frequent signs and symptoms in the acute respiratory illnesses observed are shown in Table 11 The distributions in the frequencies of the signs and symptoms were compared by the chi-square test. Among the infants of the nursery group the difference in the frequencies between illnesses with detected virus and unknown etiology was highly significant, but among the other groups the differences were not significant Among the illnesses with detected virus etiology between the infants of the nursery and family groups the difference in the frequencies was significant but it was highly significant among the illnesses with unknown etiology

Sore throat was more common in the older members of the family group than in the

durations of fever in the nursery group infants were days in the febrile illnesses both with detected virus etiology and of unknown etiology. The longest episode of fever lasting 7 days, occurred in an infant with an RS virus infection. In the infants of the family group the mean and median duration of fever were 3 days in both illness groups. Also in the infants of the nursery group the duration of fever in illnesses due to RS virus infection was the same 3 days. In the infants of the family group the fever persisted for a mean of 4 days in influenza A2 infections, and the longest fever episodes, 7 days and 6 days were observed in an adenovirus infection and one illness of unknown etiology.

In the family children aged ?—6 years the mean duration of fever was 3 days in febrile illnesses with detected virus etiology and ° days in illnesses of unknown etiology. The mean duration of fever in the influenza A2 infections was 4 days. The number of febrile illnesses among other members of the families was low.

Duration of the acute respiratory illnesses

In many illnesses, particularly in the infant groups, the duration of illness was due to the persistence of nasal discharge. The mean durations of respiratory illnesses are shown in Table 13.

The mean duration of illnesses with detected virus etiology and of unknown etiology was highly significantly longer in the infants of the nursery group than in those of the family group (t-test). In the infants of the family group the illnesses with detected virus etiology lasted longer than the corresponding illnesses in children aged 2—6 years ($p < 0.001$, t-test).

In the infants in the nursery group the duration of illnesses due to RS and adenovirus infections was longer than in the infants in the family group ($p < 0.0o$, t-test).

OTHER ILLNESSES

Only respiratory illnesses were examined and information about other infections was later obtained from the personnel in the nursery and the mothers of the families. No specimens were taken during these illnesses.

In the nursery an epidemic of rubella occurred in March 1966, when half of the infants contracted rubella. Episodes of fever without other symptoms were observed in four infants. In addition, 3 infants had diarrhea and _ cases of bacterial tonsillitis occurred.

In the infants of the family group 8 cases of rubella, 8 cases of varicella, 11 cases of measles and 3 cases of mumps occurred. Febrile episodes without other symptoms were observed in 8 infants. Diarrhea was reported

Table 13. Mc n duration of acute respiratory illnesses i days

Etiology of illness	Nursery group	Family group		
	Infants	Infants	Children 2—6 yrs	Other members
Detected virus etiology	19	14	10	10
RS virus infections	19	14	10	11
Parainfluenza virus infection	18	12	9	10
Adenovirus infections	19	13	10	8
Unknown etiology	19	12	11	8

The occurrence of fever in the acute respiratory illnesses is shown in Table 12

The frequency of fever in the illnesses was compared by the chi-square test. Among the infants of the nursery group between the illnesses with detected virus etiology and those of unknown etiology the difference in the occurrence of fever was almost significant but it was highly significant among the infants of the family group Both among the illnesses with detected virus etiology and also in the illnesses of unknown etiology the difference in the frequency of fever between the infants of the nursery and those of the family group was highly significant.

In the adenovirus infections, the difference in the frequency of fever between the infants of the nursery and family groups was highly significant. In the infants of the family group all infections with adenovirus types 1 2, 3 and 7 and even some of the type 5 infections were febrile whereas of the infants of the nursery group only a few with type 5 infections were febrile. Of the adenovirus illnesses without fever in the infants of the nursery group 10 occurred in infants aged less than 6 months and in the family group 2 occurred in infants as young as this. No febrile cases of adenovirus infections were observed in infants aged less than 8 months in the family group but two occurred in 5-month-old infants in the nursery group Among the infants of the nursery group between the illnesses due to RS parainfluenza and adenoviruses the difference in the occurrence of fever was highly significant.

In the family group the occurrence of fever in the illnesses of other children was similar to the occurrence observed in the infants. All the influenza A2 virus infections in the family infants were febrile and only 3 of the 11 influenza A2 infections in the older family members were not febrile. Among the older members a half of the adenovirus and RS virus infections were febrile.

Duration of fever The mean and median

Table 12. *Fever in the acute respiratory illnesses*

Fever	Illnesses with detected virus etiology												Illnesses of unknown etiology			
	Nursery group					Family group							Nursery group	Family group		
	Infants					Infants					Children 2—6 yrs	Other members	Infants	Infants	Children 2—6 yrs	Other members
	RS	*Parainfluenza*	*Adeno*	*Other*	Total	*RS*	*Parainfluenza*	*Adeno*	*Other*	Total	Total	Total				
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
No	3	2	29	2	36	6	6	5	1	18	13	14	106	63	43	50
Low	6	2	4	—	12	0	8	5	2	1	16	8	10	28	0	11
High	3	3	2	—	10	13	9	16	7	45	19	6	14	33	4	7
Total number of illnesses	14	7	[illegible]	2	58	25	23	26	10	84	50	28	130	124	50	68

durations of fever in the nursery group infants were days in the febrile illnesses both with detected virus etiology and of unknown etiology The longest episode of fever, lasting 7 days, occurred in an infant with an RS virus infection. In the infants of the family group the mean and median duration of fever were 3 days in both illness groups. Also in the infants of the nursery group the duration of fever in illnesses due to RS virus infection was the same 3 days. In the infants of the family group the fever persisted for a mean of 4 days in influenza A infections, and the longest fever episodes, 7 days and 6 days were observed in an adenovirus infection and one illness of unknown etiology

In the family children aged —6 years the mean duration of fever was 3 days in febrile illnesses with detected virus etiology and ? days in illnesses of unknown etiology The mean duration of fever in the influenza A infections was 4 days. The number of febrile illnesses among other members of the families was low

Duration of the acute respiratory illnesses

In many illnesses, particularly in the infant groups, the duration of illness was due to the persistence of nasal discharge The mean durations of respiratory illnesses are shown in Table 13

The mean duration of illnesses with detected virus etiology and of unknown etiology was highly significantly longer in the infants of the nursery group than in those of the family group (t-test) In the infants of the family group the illnesses with detected virus etiology lasted longer than the corresponding illnesses in children aged 2—6 years ($p < 0.001$ t-test)

In the infants in the nursery group the duration of illnesses due to RS and adenovirus infections was longer than in the infants in the family group ($p < 0.05$ t-test)

OTHER ILLNESSES

Only respiratory illnesses were examined and information about other infections was later obtained from the personnel in the nursery and the mothers of the families. No specimens were taken during these illnesses.

In the nursery an epidemic of rubella occurred in March 1966, when half of the infants contracted rubella. Episodes of fever without other symptoms were observed in four infants In addition, 3 infants had diarrhea and ? cases of bacterial tonsillitis occurred.

In the infants of the family group 8 cases of rubella, 8 cases of varicella, 11 cases of measles and 3 cases of mumps occurred. Febrile episodes without other symptoms were observed in 8 infants. Diarrhea was reported

Table 13 *Mean duration of acute respiratory illnesses in days*

Etiology of illness	Nursery group	Family group		
	Infants	Infants	Children 2—6 yrs	Other members
Detected virus etiology	19	14	10	10
RS virus infections	19	14	10	11
Parainfluenza virus infection	16	12	9	10
Adenovirus infections	19	13	10	8
Unknown etiology	19	12	11	8

from 18 infants, while bacterial tonsillitis and otitis media without respiratory symptoms were observed in 3 infants.

In the children aged 2—6 years 29 episodes of communicable diseases of childhood were reported, 13 measles, 9 varicella 5 rubella and 2 cases of mumps. Diarrhea occurred in 10 children

In the group of school-children the number of communicable diseases was 33, measles occurred in 13 children varicella in 8, rubella in 5 mumps in 6 and scarlet fever in one. These communicable diseases of childhood did not occur in major epidemics, although most of the cases were seen in the spring and fall.

Discussion

In this investigation two different groups of infants were compared. The ages of the infants differed, but it was considered impossible to maintain the mean age of the infants in the family group on the level of the infants in the nursery group. This would have been possible only with constant recruitment and release of the families. The main activity of the nursery was to provide temporary care of infants, and consequently there was only a relatively short mean observation period per infant. The number of the infants in the groups also differed. However, whenever a viral agent invaded the nursery, the opportunity to detect the infections was relatively good because of the close watch kept over the infants. Of the 2800 families with 3 or more children in the city, the number of families under surveillance comprised 1.7 per cent at the most. It was felt, however, that the group of family infants was large enough to reflect the epidemics of acute respiratory disease in the city. This was further ensured by selection of families living in different areas and by the study of the acute respiratory illnesses in the siblings and parents in the families.

The study procedure was laborious and required adaptation on the part of the families, both mothers and children. Taking the children to the outpatient clinic itself was a great inconvenience to the mothers. It is understandable that some minor illnesses were missed. Difficulties in cooperation were encountered, especially with the families in which proper care was not taken of the children. Most of the children of whom no respiratory illness was reported belonged to these families. Yet the families wanted to continue in the study when it was suggested that they should be released. Severe respiratory illnesses would certainly have been reported even in these families.

The attitude of people to this kind of long term study has been extensively described in the Cleveland study (23) and in the Virus Watch study (26). The same features were observed during this investigation. The readiness of the mothers to report respiratory illnesses varied and the reports of some mothers were invariably delayed. The idea of normal health seemed to be different and some mothers obviously accepted a child with a running nose as normal.

Comments on methods. In the family group the virus isolation specimens were sometimes taken several days after the onset of the respiratory illness and this, of course, reduced the chances of isolating the viruses responsible (7, 16). It was unexpectedly difficult to swab the pharynx in children aged 5—10 years without force and often properly taken samples were not obtained.

The tissue cultures were used in the laboratory in daily routine work. The adequacy of the methods used for isolation of adenoviruses was shown by Mäntyjärvi (44) and for isolation of RS virus by Berglund ([illegible]). In the fall of 1965, U-cells and during several periods HeLa cells showed spontaneous degeneration and detachment of cells. Because of this, the adequacy was not maintained all the time. The sensitivity of primary monkey kidney cells is considered to be sufficient for recovery of myxoviruses (12). During this investigation the growth of these cells was often poor and spontaneous detachment of

from 18 infants, while bacterial tonsillitis and otitis media without respiratory symptoms were observed in 3 infants.

In the children aged 2—6 years 29 episodes of communicable diseases of childhood were reported 13 measles, 9 varicella 5 rubella and 2 cases of mumps. Diarrhea occurred in 10 children

In the group of school-children the number of communicable diseases was 33 measles occurred in 13 children varicella in 8, rubella in 5 mumps in 6 and scarlet fever in one. These communicable diseases of childhood did not occur in major epidemics, although most of the cases were seen in the spring and fall.

of infants in the family group could have been 3 times as high as that observed during the present study The commonly reported inverse relation of respiratory illness rate and age was also observed in this study (26)

The patterns of acute respiratory illnesses in the infants of the nursery and family groups showed a somewhat similar seasonal variation. The pattern of acute respiratory illnesses in the family group did not resemble the pattern generally observed lsewhere in other geographic regions for the acute respiratory illnesses of children, with high fall and winter peaks (23, 26) In this study there was a decrease in the occurrence of acute respiratory illnesses in midwinter This may be correlated with the climate in Finland. In midwinter a very col l frost period (from —1 to —20°C) sometimes continues for months without a break. This has restricted the contacts of the infants in the family group to a minimum During this study the frost period was particularly cold and long during the winter of 1965—1966.

V rologic results. The ratio of the acute respiratory illnesses with specific virus etiology to the total number of illnesses (approximately 40 pe cent) was of the same order as in several other studies of acute respiratory infections in children (1, 14 17 33) Only in the infants of the nursery was the total positive rate lower (31 per cent)

RS virus was observed as an etiologic agent in 11 to 14 per cent of the respiratory illnesses among the infants and children of the family group and in 7 per cent of the illnesses in the infants of the nursery group. The infection rat observed in the family group was highe than that reported by Chanock and Parrott (17) but lower than in the series f Hilleman (33) and in the WHO survey f serologic studies f hospitalized patients (14) Parainfluenza viruses were observed in 7 to 11 per cent, the same rate as report l by Chanock and Parrot (17) In the infants of the nursery group the rate was low In the family group parainfluenza virus types 1 2 and 3 occurred in the ratio usually observed. Influenza A infections occurred only in one-tenth of the families, representing 2 to 7 per cent of the respiratory illnesses of the infants and children of the family group.

Acute respiratory illnesses associated with infections of adenovirus types 1—7 were observed in this long-term study in a rate hitherto only reported to occur during adenovirus epidemics. In this series, in the infants of the nursery group an adenovirus infection, proved by a significant CF or HI antibody increase and in 41 per cent of these also by an isolation, was detected in 18.6 per cent of the acute respiratory illnesses. Adenovirus type 5 was prevalent, and infections with types 1 and 2 were also frequent. In some cases, adenovirus infections were observed concurrently with RS virus infections, and 1 isolations of adenoviruses, of which one-third were sporadic, were not followed by an antibody increase.

In the infants of the family group adenoviruses were associated with 12.5 per cent of the acute respiratory illnesses. Double infections with RS and parainfluenza virus infections were observed and in addition, 6 adenoviruses not followed by a significant antibody rise were isolated. In children aged 2—6 years 17 per cent of the respiratory illnesses were associated with adenoviruses. In the family group types 1 and 5 were the commonest in infants, and types 7 and in children aged —6 years. In the older family children infections due to type 3 were frequently observed.

In the series of Laxdal *et al.* (4) the over all infection rate with adenoviruses in hospitalized patients was 11.6 per cent. Moffet *et al* (49) isolated adenoviruses in 6 per cent from infants with no symptoms of illness, but in most of these cases the viruses were recovered only from anal washings. In Sutton s study the recoveries of adenovirus types 1 2 and 5 were found to be independent of any illness in the children. The nine infants, whose sera

cells a few days after inoculation frequently occurred In addition the direct inoculation technique with the rectal swabs often caused toxic degeneration in the cells.

Berglund has shown that the diagnostic efficiency of the CF test is 86 per cent in RS virus infections of children (7) In para influenza virus infections, a heterotypic anti body response is known to occur in CF and HI tests. In children particularly with para influenza virus type 1 infection a heterotypic rise to type 3 often occurs (16 19) In this study several concurrent rises to para influenza virus types 1 and 3 were observed and if no virus was isolated the type of the parainfluenza virus infection remained undetermined

In the studies of Vargosko *et al* (71) only 19 per cent of all the infants and children from whom adenoviruses had been isolated developed an antibody rise in the CF test, yet the ratio was 39 per cent in those who had a respiratory illness and from whom adenovirus types 1 2 3 5 and 7 were isolated. Similarly in the studies of Schmidt *et al.* (60) 32 per cent of infants and young children with adenovirus type 1 2 3 and 5 isolations had a significant increase in homotypic neutralizing antibody 23 per cent in CF antibody and 20 per cent in HI antibody on kaolin treated sera. In HI tests very few heterotypic antibody increases were seen in children The sensitivity of CF test in adenovirus infections was also evaluated by Fortnov (54) In 39 per cent of the infants and children with lower respiratory disease, from whom adenovirus infections were detected by isolation and significant increase in homologous neutralizing antibody no corresponding increase in CF antibody occurred In the present study neutralizing antibodies to adenoviruses were not tested and the occurrence of adenovirus infections was based only on the results of CF and HI tests thus the importance of adenovirus may have been underestimated

The computer was of invaluable aid in the analysis of the data because of the great number of different data recorded Especially the possibility to list selected data quickly made it possible to study various aspects. In addition the dependence of the data on a great number of dates made the use of a computer necessary

Occurrence of acute respiratory illness The rates of the acute respiratory illnesses observed in this study 6.3 per person year in the infants of the nursery group 2.5 per person year in the infants of the family group and an even smaller number in the other children and parents, differed greatly from the rates found in some other studies. In the Cleveland study (23) a mean respiratory illness rate of 7 to 8 per person year was observed in the infants. In Junior Village the total illness rate was 11 per person year (5) Sutton reported a rate of 8 respiratory ill nesses per person year in a nursery (68) In the Virus Watch study a respiratory illness rate of 6 per person year was observed in children aged 0—5 years (26) The studies in the Edinburgh nursery revealed 5.2 respiratory illnesses per person year and the studies in the children s home in Kansas City 2.7 respiratory illnesses per person year (53) Backstrom-Jarvinen *et al* have studied the pattern of illnesses from birth to 5 years of 88 'model children living in Helsinki, Finland During the first year of life an incidence of 2.3 febrile respiratory illnesses was observed during the second year 1.2, in the 3rd year 1 0 in the 4th year 0 6 and in the 5th year 0 5 per person year (3) In the same nursery now studied Berglund *et al* (8) earlier observed a rate of 4 8 respiratory illnesses per person year The rate observed in the present study is somewhat higher which might be due to the special emphasis on the occurrence of acute respiratory illnesses during this study The rate of acute respiratory illnesses in the family group was probably too low because short episodes may not all have been reported, but it seems unlikely that the rate of respiratory illnesses

of infants in the family group could have been 3 times as high as that observed during the present study. The commonly reported inverse relation of respiratory illness rate and age was also observed in this study (26).

The patterns of acute respiratory illnesses in the infants of the nursery and family groups showed a somewhat similar seasonal variation. The pattern of acute respiratory illnesses in the family group did not resemble the pattern generally observed elsewhere in other geographic regions for the acute respiratory illnesses of children, with high fall and winter peaks (23, 26). In this study there was a decrease in the occurrence of acute respiratory illnesses in midwinter. This may be correlated with the climate in Finland. In midwinter a very cold frost period (from −15 to −20°C) sometimes continues for 2 months without a break. This has restricted the contacts of the infants in the family group to a minimum. During this study the frost period was particularly cold and long during the winter of 1965—1966.

Virologic results. The ratio of the acute respiratory illnesses with specific virus etiology to the total number of illnesses (approximately 40 per cent) was of the same order as in several other studies of acute respiratory infections in children (1, 14, 17, 33). Only in the infants of the nursery was the total positive rate lower (31 per cent).

RS virus was observed as an etiologic agent in 11 to 14 per cent of the respiratory illnesses among the infants and children of the family group and in 7 per cent of the illnesses in the infants of the nursery group. The infection rate observed in the family group was higher than that reported by Chanock and Parrott (17) but lower than in the series of Hilleman (33) and in the WHO survey of serologic studies of hospitalized patients (14). Parainfluenza viruses were observed in 7 to 11 per cent, the same rate as reported by Chanock and Parrott (17). In the infants of the nursery group the rate was lower. In the family group parainfluenza virus types 1, 2 and 3 occurred in the ratio usually observed. Influenza A2 infections occurred only in one-tenth of the families, representing 3 to 7 per cent of the respiratory illnesses of the infants and children of the family group.

Acute respiratory illnesses associated with infections of adenovirus types 1—7 were observed in this long-term study in a rate hitherto only reported to occur during adenovirus epidemics. In this series, in the infants of the nursery group an adenovirus infection, proved by a significant CF or HI antibody increase and in 71 per cent of these also by an isolation, was detected in 18.6 per cent of the acute respiratory illnesses. Adenovirus type 5 was prevalent and infections with types 1 and 2 were also frequent. In some cases, adenovirus infections were observed concurrently with RS virus infections, and 12 isolations of adenoviruses, of which one-third were sporadic, were not followed by an antibody increase.

In the infants of the family group, adenoviruses were associated with 12.5 per cent of the acute respiratory illnesses. Double infections with RS and parainfluenza virus infections were observed and in addition, 6 adenoviruses not followed by a significant antibody rise were isolated. In children aged 2—6 years 17 per cent of the respiratory illnesses were associated with adenoviruses. In the family group types 1 and 5 were the commonest in infants, and types 7 and 2 in children aged 2—6 years. In the older family children infections due to type 3 were frequently observed.

In the series of Laxdal et al. (4) the over all infection rate with adenoviruses in hospitalized patients was 11.6 per cent. Moll et al. (49) isolated adenoviruses in 6 per cent from infants with no symptoms of illness, but in most of these cases the viruses were recovered only from anal washings. In Sutton's study the recoveries of adenovirus types 1, 2 and 5 were found to be independent of any illness in the children. The nine infants, whose sera

were tested already had CF antibodies and neutralizing antibodies to the types of adenoviruses recovered In the present study the adenovirus isolations not followed by a significant antibody rise were not included in the etiologic group and their significance remained obscure

Clinical features Among the infants of the nursery group lower respiratory tract infections (LRI) were observed more often in the illnesses associated with detected virus etiology than in the illnesses with unknown etiology This was due to RS and parainfluenza virus infections. In both groups of infants, adenovirus infections were mainly associated with upper respiratory tract illnesses (URI) In illnesses of unknown etiology LRI was diagnosed more often in the infants of the family group than in the infants of the nursery group This may possibly indicate inadequacy of the sampling procedure in the infants of the family group

The illnesses with detected virus etiology were more often febrile than the illnesses of unknown etiology This was due to RS and parainfluenza virus infections in the infants of the nursery group but in the infants of the family group most of the adenovirus infections were likewise febrile. This might be associated with the fact that the occurrence of adenovirus types varied in these groups but also with the difference in the ages. On the other hand febrile illnesses were certainly more readily reported in the family group than minor illnesses without fever Of the illnesses with unknown etiology more were febrile in the infants of the family group than in those of the nursery group and this also suggests that the illnesses were due to the agents studied even though the virologic identification was missed

Similarly the survey of the signs and symptoms emphasized the importance of the agents studied Otitis media was more common in the illnesses with detected virus etiology than in the illnesses of unknown etiology among the infants of the nursery group In the infants of the family group otitis media was often found in RS and parainfluenza virus infections. Cough, laryngeal symptoms and cervical lymphadenopathy were observed more often and rhonchi less often in the illnesses with detected virus etiology In the illnesses with unknown etiology rhonchi and otitis media were observed more often in the infants of the family group than in those of the nursery group

The duration of all acute respiratory illnesses was longer in the infants of the nursery group than in those of the family group.

Outbreaks of virus infections RS virus infections occurred in outbreaks, in the family group during both fall periods but in the nursery as a single outbreak, when all the infants contracted the infection. In addition a single outbreak of parainfluenza virus infection due to type 3 was observed in the nursery at a time when this infection was prevalent in the infants and children of the families studied. Once in both infant groups the occurrence of illnesses associated with adenoviruses was observed at the same time. The outbreaks of adenovirus types 2, 5 and 7 in the nursery were not correspondingly observed in the family group Outbreaks due to other parainfluenza viruses, influenza A2, and Coxsackie B type 2 in the family group were not noticed in the infants of the nursery group

In conclusion it can be pointed out that the infants in the nursery studied represented a group with a high respiratory illness rate characterized by frequent adenovirus infections Only occasionally did the viruses causing acute respiratory illness in the family children invade the nursery at the same time. Accordingly such isolated nurseries are not representative index populations for the acute respiratory illnesses in the surrounding community By a surveillance of even a small group of families more virus infections can be detected and such a group propably more nearly reflects the epidemiologic pattern of acute viral respiratory infections in a community

Summary

The significance of respiratory syncytial (RS) parainfluenza, influenza and adenoviruses in the etiology of acute respiratory disease in children was evaluated and the value of a group of institutionalized children as an index of the respiratory disease among children in the *surrounding community* was studied by a long term survey The population in the two study groups consisted of families including at least one infant and of infants residing in a nursery in the same city The mean number of infants in the nursery was 15 and in the families 40

All acute respiratory illnesses occurring *during the* year surveillance were studied by virus isolation, serologic tests and clinical examination. The total observation time for infants in the nursery group was 34 person-*months and 1031 person-months for the in*fants in the family group. The total person months observed in the family group were 4077

A *total of 599 acute respiratory illnesses* ere studied and virus etiology was established in 40 per cent of the 410 illnesses in the family group and in 31 per cent of the 188 illnesses in the *nursery group.*

In the infants f the nursery group the rate of respiratory illnesses was 6 3 per person-year In the infants of the family group the illness rate 5 per person ear was only about one third of the rate in the nursery The mean prevalence f respiratory symptoms was 39 *per cent in the infants f* the nursery group and 10 per cent in the infants of the family group On average at any one time infants in the nursery and 4 infants in the family group had respirat ry illness symptoms.

The highest incidence of acute respiratory illnesses occurred in the fall and the spring and an unexpectedly low incidence was observed in the family group during the frost period in midwinter

In the infants of the nursery group, per cent of the illnesses were associated with RS virus, 4 per cent with parainfluenza virus type 3 and 19 per cent with adenoviruses, mainly with types 5 and 2. In the infants of the family group, 1 per cent of the illnesses were associated with RS virus, 11 per cent with parainfluenza, per cent with influenza A2, and 12 per cent with adenoviruses.

The clinical observations further emphasized the *importance* of these viruses in the respiratory disease of children. Among the infants of the nursery RS virus and parainfluenza viruses were found to cause in*volvement of the lower respiratory* tract (LRI) more often than the unknown etiologic agents. The illnesses with detected virus etiology were more often febrile than the *illnesses of unknown etiology Otitis media* was observed more often in illnesses with detected virus etiology in the infants of the nursery group this was due to RS virus *infections. In the infants of* the family group otitis media occurred in RS and parainfluenza virus infections, but also in illnesses with unknown etiology

In the outbreaks of acute respiratory illness identical etiology was seen *only once*, when the parainfluenza virus type 3 was simultaneously prevalent as a sudden outbreak in *both groups*. Two RS virus outbreaks occurred in the families in both *fall* seasons, but only one RS outbreak occurred in the nursery In the nursery outbreaks of adeno*virus types* _, 5 and 7 occurred and corre-

sponding outbreaks were not seen in the families. The outbreaks of parainfluenza virus types 1 2 influenza A2 and Coxsackie B type 2 were not noticed to occur in the nursery and adenovirus type 3 did not occur In both groups, in a third of the outbreaks the etiology remained totally unknown.

The conclusion is drawn that the infants in the nursery studied were a group with a high respiratory illness rate and frequent adenovirus infections due to different adenovirus types than those observed in the families. The viruses causing acute respiratory illnesses in the children of families in the surroundings only occasionally invaded the nursery at the same time. Thus such isolated groups of institutionalized children as the infants in the nursery studied are not representative index populations for respiratory disease in the children of the community as a whole

Acknowledgments

I am deeply grateful to Professor Pekka Halonen, M.D., Head of the Department of Virology, for the continuous support he has given me during this study. It was he who introduced me to virology and his extensive knowledge and experience in the field of respiratory viruses have been of invaluable help to me. He has placed the resources of his laboratory at my disposal and permitted his staff to assist me. In the preparation of the manuscript his criticism has been of great help.

I am grateful to Professor Tuomas Peltonen, M.D., Head of the Children's Hospital, University of Turku, my teacher in pediatrics, for his encouragement. He and Professor Halonen together suggested this subject to me. Professor Peltonen allowed me to use the facilities of the outpatient clinic in his hospital for collection of specimens.

I am greatly indebted to Professor Johan Wickström, M.D., Head of the Hospital for Infectious Diseases in Turku. As an assistant physician in his hospital I first had an opportunity to participate in research work concerning the respiratory infections of children. As physician-in-charge he allowed me to collect specimens from the Nursery.

I record my indebtedness to the late Associate Professor Jarl Axel Grönroos, M.D., Department of Medical Microbiology, University of Turku, for co-operation, friendship and interest for my work.

I am grateful to Associate Professor Kauko Kouvalainen, M.D., Children's Hospital, University of Turku, for his criticism of the manuscript.

I wish to express my gratitude to my colleagues at the Department of Virology for their help and interest during my work. I am much obliged to Dr Rauno Mäntyjärvi, M.D., for his advice on problems of virology and his criticism of the manuscript and to Dr Bo Berglund, M.D., for co-operation and advice based on his extensive knowledge of respiratory syncytial virus.

I wish to thank the personnels of the Department of Virology, the Outpatient Clinic of the Children's Hospital, and the Nursery and the health sisters at the Child Welfare Centers for their assistance and courtesy. In particular I am grateful to Mrs. Leena Nurmi for technical assistance during the whole study, Mrs. Maija Aro and Mrs. Sirkka-Liisa Koskinen for their secretarial assistance.

My sincere thanks are due to the families which participated in this study.

I am grateful to Mr. Pekka Aho, M.Sc., Institute of Applied Mathematics, University of Turku, for programing the data processing, Mrs. Aili Ryynänen, M.A., and her assistant at the Library of the Medial Faculty, University of Turku, for their help in collecting the literature, and Mrs. Jean Margaret Perttunen, B.Sc., for revising the language of the manuscript.

This study was personally supported by the National Research Council for Medical Sciences. Grants from the Finnish Federation of University Women and the Foundation for Paediatric Research in Finland are gratefully acknowledged. The technical side of the work has been supported by grants to the institution from the Sigrid Jusélius Foundation.

Turku, February 1969

Leena Vihma

sponding outbreaks were not seen in the families. The outbreaks of parainfluenza virus types 1 2 influenza A2 and Coxsackie B type 2 were not noticed to occur in the nursery and adenovirus type 3 did not occur In both groups, in a third of the outbreaks the etiology remained totally unknown.

The conclusion is drawn that the infants in the nursery studied were a group with a high respiratory illness rate and frequent adenovirus infections due to different adenovirus types than those observed in the families. The viruses causing acute respiratory illnesses in the children of families in the surroundings only occasionally invaded the nursery at the same time. Thus such isolated groups of institutionalized children as the infants in the nursery studied are not representative index populations for respiratory disease in the children of the community as a whole.

Acknowledgments

am deeply grateful to Professor Pekka Halonen, M.D., Head of the Department of Virology for the continuous support he has given me uring this study. It was he who introduced e to virology and his extensive knowledge nd experience in the field of respiratory iruses have been of invaluable help to me. le has placed the resources of his laboratory t my disposal and permitted his staff to ssist me. In the preparation of the manuscript his criticism has been of great help.

I am grateful to Professor Tuomas Peltonen, M.D., Head of the Children's Hospital, University of Turku, my teacher in pediatrics, for his encouragement. He and Professor Halonen together suggested this subject to me. Professor Peltonen allowed me to use the facilities of the outpatient clinic in his hospital for collection of specimens.

I am greatly indebted to Professor Johan Wikström, M.D., Head of the Hospital for Infectious Diseases in Turku. As an assistant physician in his hospital I first had an opportunity to participate in research work concerning the respiratory infections of children. As physician-in-charge he allowed me to collect specimens from the Nursery.

I record my indebtedness to the late Associate Professor Jarl Axel Grönroos, M.D., Department of Medical Microbiology, University of Turku, for co-operation, friendship and interest for my work.

I am grateful to Associate Professor Kauko Kouvalainen, M.D., Children's Hospital, University of Turku, for his criticism of the manuscript.

I wish to express my gratitude to my colleagues at the Department of Virology for their help and interest during my work. I am much obliged to Dr Rauno Mäntyjärvi, M.D., for his advice on problems of virology and his criticism of the manuscript and to Dr Bo Berglund, M.D., for co-operation and advice based on his extensive knowledge of respiratory syncytial virus.

I wish to thank the personnels of the Department of Virology, the Outpatient Clinic of the Children's Hospital, and the Nursery and the health sisters at the Child Welfare Centers for their assistance and courtesy. In particular I am grateful to Mrs. Leena Nurmi for technical assistance during the whole study, Mrs. Maija Aro and Mrs. Sirkka Liisa Koskinen for their secreterial assistance.

My sincere thanks are due to the families which participated in this study.

I am grateful to Mr. Pekka Aho, M.Sc., Institute of Applied Mathematics, University of Turku, for programing the data processing, Mrs. Aili Ryynänen, M.A., and her assistant at the Library of the Medial Faculty, University of Turku, for their help in collecting the literature, and Mrs. Jean Margaret Perttunen, B.Sc., for revising the language of the manuscript.

This study was personally supported by the National Research Council for Medical Sciences. Grants from the Finnish Federation of University Women and the Foundation for Paediatric Research in Finland are gratefully acknowledged. The technical side of the work has been supported by grants to the institution from the Sigrid Jusélius Foundation.

Turku, February 1969

Leena Vihma

sponding outbreaks were not seen in the families. The outbreaks of parainfluenza virus types 1 2, influenza A2 and Coxsackie B type 2 were not noticed to occur in the nursery and adenovirus type 3 did not occur In both groups, in a third of the outbreaks the etiology remained totally unknown.

The conclusion is drawn that the infants in the nursery studied were a group with a high respiratory illness rate and frequent adenovirus infections due to different adenovirus types than those observed in the families. The viruses causing acute respiratory illnesses in the children of families in the surroundings only occasionally invaded the nursery at the same time. Thus such isolated groups of institutionalized children as the infants in the nursery studied are not representative index populations for respiratory disease in the children of the community as a whole.

Acknowledgments

I am deeply grateful to Professor Pekka Halonen, M.D., Head of the Department of Virology, for the continuous support he has given me during this study. It was he who introduced me to virology and his extensive knowledge and experience in the field of respiratory viruses have been of invaluable help to me. He has placed the resources of his laboratory at my disposal and permitted his staff to assist me. In the preparation of the manuscript his criticism has been of great help.

I am grateful to Professor Toomas Peltonen, M.D., Head of the Children's Hospital, University of Turku, my teacher in pediatrics, for his encouragement. He and Professor Halonen together suggested this subject to me. Professor Peltonen allowed me to use the facilities of the outpatient clinic in his hospital for collection of specimens.

I am greatly indebted to Professor Johan Wikström, M.D., Head of the Hospital for Infectious Diseases in Turku. As an assistant physician in his hospital I first had an opportunity to participate in research work concerning the respiratory infections of children. As physician-in-charge, he allowed me to collect specimens from the Nursery.

I record my indebtedness to the late Associate Professor Jari Axel Grönroos, M.D., Department of Medical Microbiology, University of Turku, for co-operation, friendship and interest to my work.

I am grateful to Associate Professor Kauko Kouvalainen, M.D., Children's Hospital, University of Turku, for his criticism of the manuscript.

I wish to express my gratitude to my colleagues at the Department of Virology for their help and interest during my work. I am much obliged to Dr Rauno Mäntyjärvi, M.D., for his advice on problems of virology and his criticism of the manuscript and to Dr Bo Berglund, M.D., for co-operation and advice based on his extensive knowledge of respiratory syncytial virus.

I wish to thank the personnels of the Department of Virology, the Outpatient Clinic of the Children's Hospital, and the Nursery and the health sisters at the Child Welfare Centers for their assistance and courtesy. In particular I am grateful to Mrs. Leena Nurmi for technical assistance during the whole study, Mrs. Maija Aro and Mrs. Sirkka Liisa Koskinen for their secreterial assistance.

My sincere thanks are due to the families which participated in this study.

I am grateful to Mr Pekka Aho, M.Sc., Institute of Applied Mathematics, University of Turku, for programing the data processing, Mrs. Aili Ryynänen, M.A., and her assistant at the Library of the Medical Faculty, University of Turku, for their help in collecting the literature and Mrs. Jean Margaret Perttunen, B.Sc., for revising the language of the manuscript.

This study was personally supported by the National Research Council for Medical Sciences. Grants from the Finnish Federation of University Women and the Foundation for Paediatric Research in Finland are gratefully acknowledged. The technical side of the work has been supported by grants to the institution from the Sigrid Jusélius Foundation.

Turku, February 1969.

Leena Vihma

References

1. Aitken, C. J. D., Moffat, M. A. J. & Sutherland, J. A. W.: Respiratory illness and viral infection in an Edinburgh nursery. *J Hyg (Camb) 65*: 25, 1967.
2. Babb, J. M., Stoneman, M. E. R. & Stern, H.: Myocarditis and croup caused by Coxsackie virus type B5, *Arch Dis Child 36*: 551, 1961.
3. Bäckström-Järvinen, L., Tiisala, R., Kantero, R. L. & Hallman, N.: Illnesses among normal Finnish children during the first five years of life. *Ann Paed Fenn 12*: 13, 1966.
4. Beale, A. J., McLeod, D. L., Stackiw, W. & Rhodes, A. J.: Isolation of cytopathogenic agents from the respiratory tract in acute laryngotracheobronchitis, *Brit Med J I*: 302, 1958.
5. Bell, J. A., Huebner, R. J., Rosen, L., Rowe, W. P., Cole, R. M., Mastrota, F. M., Floyd, T. M., Chanock, R. M. & Shvedoff, R. A.: Illness and microbial experiences of nursery children at Junior Village. *Amer J Hyg 74*: 267, 1961.
6. Bergamini, F., Spinozzola, M. & Giannelli, F.: Studio epidemiologico e virologico di un episodio epidemico di malattia minore da virus ECHO 9 (Coxsackie A 23) in una comunità infantile, *Boll Ist Sieroter Milan 46*: 190, 1967.
7. Berglund, B.: Studies on respiratory syncytial virus infection, *Acta Paediat Scand* Suppl. *176*, 1967.
8. Berglund, B. & Mäntyjärvi, R.: Respiratory infections in children at a nursery in Finland. Virological and epidemiological studies over a 1 month period, *Ann Paed at Fenn, 12*: 143, 1966.
9. Berglund, B., Mäntyjärvi, R. & Salmi, A.: Neutralizing, complement fixing and precipitating antibody response of guinea pigs to intranasal and intracardiac respiratory syncytial virus inoculations, *Ann Med Exp Biol Fenn 45*: 193, 1967.
10. Berglund, B., Vihma, L. & Wickström, J.: Respiratory syncytial virus studies on children hospitalized during an outbreak of respiratory illness in Finland, *Amer J Epidem 81*: 271, 1965.
11. Carmichael, J., McGuckin, R. & Gardner, P. S.: Outbreak of Coxsackie type B virus in a children's home in Newcastle Upon Tyne, *Brit Med J II*: 535, 1963.
12. Canchola, J. G., Chanock, R. M., Jeffries, B. C., Christmas, E. E., Kim, H. W., Vargosko, A. J. & Parrott, R. H.: Recovery and identification of human myxoviruses, *Bact Rev 29*: 496, 1965.
13. Chanock, R. M.: Association of a new type of cytopathogenic myxoviruses with infantile croup, *J Exp Med 104*: 555, 1956.
14. Chanock, R., Chambon, L., Chang, W., Gonçalves Ferreira, F., Gharpure, P., Grant, L., Hatem, J., Imam, I., Kalra, S., Lim, K., Madalengoitia, J., Spence, L., Teng, P. & Ferreira, W.: WHO respiratory disease survey in children. A serological study, *Bull WHO 37*: 363, 1967.
15. Chanock, R. M., Cook, M. K., Fox, H. H., Parrott, R. H. & Huebner, R. J.: Serological evidence of infection with Eaton agent in lower respiratory illness in childhood. *New Engl J Med, 262*: 648, 1960.
16. Chanock, R. M. & Johnson, K. M.: Parainfluenza viruses. *In* Lennette, E. H. & Schmidt, N. J. (eds.): *Diagnostic Procedures for Viral and Rickettsial Diseases.* Amer Publ Health, New York 1964, 3rd ed. p. 478.
17. Chanock, R. M. & Parrott, R. H.: Acute respiratory disease in infancy and childhood: Present understanding and prospects for prevention, *Pediatrics 36*: 21, 1965.
18. Chanock, R. M., Parrott, R. H., Cook, K., Andrews, B. E., Bell, J. A., Reichelderfer, T., Kapikian, A. Z., Mastrota, F. M. & Huebner, R. J.: Newly recognized myxoviruses from children with respiratory disease, *New Engl J Med, 258*: 207, 1958.
19. Chanock, R. M., Parrott, R. H., Johnson, K. M., Kapikian, A. Z. & Bell, J. A.: Myxoviruses: Parainfluenza, *Amer Rev Resp Dis 88*: 152, 1963.
20. Chanock, R. M., Roizman, B. & Myers, R.: Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization, *Amer J Hyg 66*: 281, 1957.
21. Couvreur, J. & Gerbeaux, J.: Intérêt des méthodes d'enquêtes virologiques longitudinales dans les collectivités circonscrites. Bilan de trois années de recherches faites au Centre de Pneumo-Phtisiologie Infantile de l'hôpital Léo Bernard, *Bull Soc Med Hôp 115*: 1231, 1964.
22. Davenport, F. M. & Minuse, E.: Influenza viruses.

In Lennette E. H. & Schmidt, N. J. (eds) *Diagnostic Procedures for Viral and Rickettsial Diseases.* Amer Publ Health, New York 1964, 3rd ed, p. 463.

22. Dingle J. H., Badger, G. F. & Jordan, W. S. J.: *Illness in the Home. A study of 25000 Illnesses in a Group of Cleveland Families.* Press of Western Reserv. University. Cleveland 1964.

23. Elveback, L. R., Fox, J. P., Ketler A., Brandt, C. D., Wassermann, F. E. & Hall, C. E.: The Virus Watch Program. A continuing surveillance of viral infections in metropolitan New York families. III Preliminary report on association of infections with disease. *Amer J Epidem 83* 436, 1966.

24. Forsell, P., Halonen, H., Stenström, R., Jansson, E. & Wager O.: An adenovirus epidemic due to types 1 and 2, *Ann Paediat Fenn, 8* 33, 1962.

25. Fox, J. P., Elveback, L. R., Spigland, I., Frothingham, T. E., Stevens, D. A. & Huger, M.: The Virus Watch Program. A continuing surveillance of viral infections in metropolitan New York families. I Overall plan, methods of collecting and handling information and summary report of specimens collected and illnesses observed, *Amer J Epidem, 83* 389, 1966.

27. Glezen, W. P., Thornburg, G., Chin, T. D. Y. & Wenner H. A.: Significance of Mycoplasma infections in children with respiratory disease *Pediatrics, 39* 516, 1967.

28. Grayston, J. T., Alexander E. R., Kenny G. E., Clarke F. R., Fremont, J. C. & MacColl, W. A.: Mycoplasma pneumoniae infections. Clinical and epidemiological studies, *JAMA 191* 369, 1965.

29. Grönroos, J. A., Vihma, L., Salmivalli, A. & Berglund, B.: Coexisting viral (respiratory syncytial) and bacterial (pneumococcus) otitis media in children, *Acta Otolaryng (Stockholm) 65* 505, 1968.

30. Hammon, W. McD. & Work, T. H.: Arbovirus infection in man. *In* Lennette E. H. & Schmidt, N. J. (eds) *Diagnostic Procedures for Viral and Rickettsial Diseases.* Amer Publ Health, New York 1964 3rd ed. p. 293.

31. Halonen, P. E., Ryan, J. M. & Stewart, J. A.: Rubella hemagglutinin prepared with alkaline extraction of virus grown in suspension culture of BHK 21 cells, *Proc Soc Biol Med, 125* 162, 1967.

32. Harris, D. J., Wulff H., Ray C. G., Poland, J. D., Chin, T. D. Y. & Wenner H. A.: Viruses and disease. II. An outbreak of parainfluenza type 2 in a children's home, *Amer J Epidem, 87* 419, 1968.

33. Hilleman, M. R., Hamparian, V. V., Ketler, A., Reilly, C. M., McClelland, L., Cornfeld, D. & Stokes, J. J.: Acute respiratory illnesses among children and adults. Field study of contemporary importance of several viruses and appraisal of the literature *JAMA 180* 445, 196...

34. Hornsleth, A.: Respiratory virus disease in infancy and childhood in Copenhagen 1963—1965. An estimation of the etiology based on complement fixation tests. *Acta Path Microbiol Scand, 69* 287, 1967.

35. Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H. & Bell, J. A.: Adenoidal-pharyngeal-conjunctival agents. A newly recognized group of common viruses of the respiratory system, *New Engl J Med, 251* 1077, 1954.

36. Jansson, E.: Preparation of complement fixing antigen for routine use in diagnosis of Eaton pneumonia, *J Clin Path, 17* 435, 1964.

37. Jansson, E. & Wager O.: Adenovirus antibodies in patients with respiratory infection, *Ann Med Intern Fenn, 50* 221, 1961.

38. Jansson, E., Wager O., Forssell, P. & Stenström, R.: Epidemic occurrence of adenovirus type 7 infection in Helsinki, *Ann Paediat Fenn 8* 24, 1962.

39. Kapikian, A. Z., Bell, J. A., Mastrota, F. M., Johnson, K. M., Huebner R. J. & Chanock, R. M.: An outbreak of febrile illness and pneumonia associated with respiratory syncytial virus infection, *Amer J Hyg 74* 234, 1961.

40. Kendall, E. J. C., Bynoe M. L. & Tyrrell, D. A. J.: Virus isolations from common colds occurring in a residential school, *Brit Med J II* 82, 1962.

41. Korshunova, M. P. & Ponomareva, T. L.: Clinical aspects of syncytial respiratory infection in institutionalized infants, *Pediatria, 46* 149, 1967.

42. Laxdal, O. E., Robertson, H. E., Braaten, V. & Walker W. A.: Acute respiratory infections in children. I An intensive study of the etiology in one community *C and M A Am J 88* 1049, 1963.

43. Loda, F. A., Clyde W. A. J., Glezen, W. P., Senior R. J., Sheaffer C. I. & Denny F. W. J.: Studies on the role of viruses, bacteria and M. pneumoniae as causes of lower respiratory tract infections in children, *J. of Pediat 72* 161, 1968.

44. Mäntyjärvi, R.: Adenovirus infections in servicemen in Finland, *Ann Med Exp Biol Fenn, 44* suppl. 4, 1966.

45. Mäntyjärvi, R.: Precipitating antibody response to herpes simplex virus in rabbits after herpetic keratoconjunctivitis, *Acta Path Microbiol Scand, 65* 361, 1965.

46. Mansell, C. C., Lengyel, M. B., Hilleman, M. R., Warfel, R. E. & Stokes, J. J.: Echovirus in-

fection in nursery and kindergarten children. New rhinovirus serotype 54 *Proc Soc Exp Biol Med, 124* 845 1967

47 Medical Research Council Working Party on Acute Respiratory Virus Infections. A collaborative study of the aetiology of acute respiratory infections in Britain 1961—4 *Brit Med J II:* 319 1965.

48. Melnick, J L., Wenner H A. & Rosen, L. The Enteroviruses. *In* Lennette E. H & Schmidt M J (eds): *Di gnost c Procedures for V ral and Pickettsial Diseases.* Amer Publ Health New York 1964 3rd ed.

49 Moffet H L. & Cramblett H G. Viral isolations and illnesses in young infants attending a well baby clinic, *New E gl J Med* 67 1 13 1962.

50 Morozenko, M L.: A study of respiratory syncytial infection in young infants, *V p Okh Materin Dets 12:* 10: 8, 1967

51 Morris, J A Blount J E. Jr & Savage R. E. Recovery of cytopathogenic agent from chimpanzees with coryza, *Proc Soc Exp Biol Med 92* 544 1956.

5_ Philipson, L. & Wesslén, T Recovery of a cytopathogenic agent from patients with non liphtheric croup n l from lay nursery children. I Properties of the agent *Arch v Ges Virusforsch 8* 7 1958.

53. Poland J D Wulff H., Welt n, E. R., Kidd, P Chin T D Y & W nner H A Viruses and disease: Studies in an childrens home *Amer J Epidem 84:* 92, 1966.

54. Portnoy B., Salvatore M A., Hanes, B., Hamme D I Leedom, J M Jambazian, A. & Eckert H A The sensitivity of the complement fixation test for the detection of adenovirus infections in infants and children with lower respiratory disease *Amer J Epidem 86* 362, 1967

55. Rauhala, Urho: *S omala nen yhteisk anan sosiaalinen kerrostuneisuus* (The social stratification of Finnish society) Werne Söderström, Porvoo 1966.

56. Rose H. M The Adeno iruses. *In* Lennett L. H & Schmidt N J (eds.) *Diagnost c Procedures fo V r l and R ckettsial Disease* Amer Publ Health, New Yo k 1964 3rd ed.

57 Rosen, L., Ho is, J F Mastrota F M Bell, J A. & Huebner R. J : An utbreak of infection with a Type 1 reovirus among children i an institution, *Amer J Hyg 71* 266, 1960.

58. Rosen, L., Johnson, J H., Huebner R. J & Bell, J A. Observations on a newly recognized ECHO virus and a descriptio of a outbreak in nursery *Amer J Hyg 67:* 300, 1958.

59 Saito, M., Shinozaki, I Nakamura K N ga hama, H. & Minamitani, M.: Epidemic cases c respiratory syncytial virus infection in a nursery I Epidemiological and clinical studies, *Med Bu* (Tokyo) *4:* 278, 1967

60 Schmidt N J Lennette E. H. & King, C. J Neutralizing, hemagglutination-inhibiting and group complement fixing antibody responses in human adenovirus infections, *J Immun 97* 64, 1966.

61 Sever J L.: Application of a microtechnique to viral serological investigations, *J Immun, 88* 320 196_

6_ Sohier R., Chardonnet Y & Prunieras, M.: Adenoviruses. Status of current knowledge *Progr Med V ol 7:* _33, 1965.

63. Spigland, I., Fox, J P Elveback, I R., Wassermann, F E., Ketler A Brandt C. D. & Kogon, A : The Virus Watch Program: A continuing surveillance of viral infections in metropolitan New York families. II Laboratory methods and preliminary report on infections revealed by virus isolation, *Amer J Epidem 83* 413, 1966.

64 Sterne G. Infections with adenovirus type 1 in children and their relationship to acute respiratory disease *Acta Paed at Scand 48:* _87 1959.

65. Sterner G de Hevesy G Tunevall, G. & Wolontis, S. Acute respiratory illness with Mycoplasma pneumo iae. An outbreak in a home for children, *Acta Paediat Scand 55:* 280, 1966.

66. Sterner G., Wolontis, S., Bloth, B. & de Hevesy G Respiratory syncytial virus. An outbreak of acute respiratory illnesses in a home f r infants, *Acta Paediat Scand 55:* 273, 1966.

67 Stuart Harris, C. H. *I fl enza d ther V rus Infections of the Respiratory tract* Edward Arnold lt l, London 1965, 2nd ed.

68. Sutton, R. N P Respiratory viruses in a residential ursery *J Hyg (C mb) 60:* 51 1962.

69 Tyrrell, D A. J *C mm Colds and R lated Diseases* Edward Arnold ltd, Lo do 1965.

70 Vargosko, A J Kim, H W Parrott R. H & Cha ock, R. M Associatio f C xsa kie B5 rus with minor respirat ry tract illness i hildren, *Amer J Dis Ch ld 104* 530, 1962.

71 V rgosko, A J Kim, H W Parrott R. H J ffries, B. C., W g D & Chanock, R. M.: Reco ry and identification f denovirus in infections of infants and hildren, *Bact Rev 29:* 487 1965.

7_ va der Veen, J : The role f deno iruses i respiratory diseases, *Amer R Resp Dis 88* 167 1963.

3. Wolontis, S., Tunev ll, G & Sterner G Adenovirus type 5 infections. A outbreak of febrile pharyngitis in a home f infants, *A ta Paediat Scand 56* 57 1967

fection in nursery and kindergarten children. New rhinovirus serotype 54 *Proc Soc Exp Biol Med, 124*: 845, 1967
47 Medical Research Council Working Party on Acute Respiratory Virus Infections. A collabora tive study of the aetiology of acute respiratory infections in Britain 1961—4 *Brit Med J II*: 319 1965.
48. Melnick, J L., Wenner H. A. & Rosen, L.: The Enteroviruses. *In* Lennette, E. H. & Schmidt, M. J (eds): *Diagnostic Procedures for Viral and Rickettsial Diseases.* Amer Publ Health New York 1964 3rd ed.
49. Moffet H L. & Cramblett H. G Viral isolations and illnesses in young infants attending a well baby clinic, *New Engl J Med 267*: 1 13, 1962.
50 Morozenko, M A. A study of respiratory syncytial infection in young infants, *V p Okhr Materin Dets 12* 10: 8, 1967
51 Morris, J A., Blount J E. J & Savage R. E. Recovery of ytopathogenic agent from chimpan zees with coryza, *Proc Soc Exp Biol Med 92* 544 1956.
52 Philipson L. & Wesslén T: Recovery of a ytopathogenic gent from patients with non-diph theric croup and from day ursery children. I Properties of the agent *Arch v Ges Virusf rsch 8*: 7" 1958.
53. Poland, J D Wulff H., W lton, E. R., Kidd, P Chin T D Y & Wenner H A. Viruses and disease Studies in an children s home *Amer J Epidem 84*: 92, 1966.
54 Portnoy B Salvatore M A., Hanes, B., Hammer D I Leedom, J M Jambarian, A. & Eckert H. A.: The sensitivity of the complement fixation test for the detectio of adeno irus infections in infants and children with lower respiratory disease *Amer J Epidem 86*: 362, 1967
55. Rauhala, Urho *Suomalainen yhteiskun an sosiaa linen kerrostuneisuus* (The social stratification of Finnish society) Werner Söd rström, Porvoo 1966.
56. Rose, H M The Adenoviruses. *In* Lennette E. H & Schmidt, N J (eds.) *Diagnost c Procedures f V ral and Rickettsial Diseases.* Am Publ Health, New York 1964 3rd ed.
57 Rosen, L., Hovis, J F Mastrota F M., Bell, J A. & Huebner R. J: An outbreak of infection with a Type 1 reo irus mong children in an institution, *Amer J Hyg 71* 266, 1960
58. Rosen, L., Johnson, J H Huebne R. J & Bell, J A. Observations n newly recognized ECHO irus and a descripti of an utbreak in a ursery *Amer J Hyg 67* 300, 1958.
59 Saito, M Shinozaki, I Nakamura, K Naga hama, H & Minamitani, M. Epidemic cases f respiratory syncytial virus infection in a nursery I Epidemiological and clinical studies, *Med Biol* (Tokyo) *74*: 278, 1967
60. Schmidt N J., Lennette E. H. & King, C. J Neutralizing, hemagglutination inhibiting and group complement fixing antibody responses in human adenovirus infections, *J Immun 97*: 64 1966.
61. Sever J L. Application of a microtechnique to viral serological investigations, *J Immun, 88* 320, 1962.
62. Sohier R., Chardonnet Y & Prunieras, M. Adenoviruses. Status of current knowledge *Progr Med Virol, 7* 233, 1965.
63. Spigland, I., Fox, J P Elveback, L. R., Wasser mann, F E., Ketle A., Brandt C. D & Kogon, A. The Virus Watch Program: A co tinuing surveillance of viral infections in metropolitan New York families. II. Laboratory methods and preliminary report on infections revealed by irus isolation, *Amer J Epidem 83*: 413 1966.
64 Sterner G.: Infections with adenovirus type in children and their relationship to acute respiratory disease *Acta Paediat Scand 44* 237 19.9.
65. Sterner G de Hevesy G Tunevall, G & W lontis, S. Acute respiratory illness with Myco plasma pneumoniae An o tbreak i a home for children, *Acta Paed at Scand, 55*: 280 1966.
66. Sterner G Wolontis, S., Bloth, B. & de Hevesy G: Respiratory syncytial irus. A outbreak of cut respiratory illnesses in a home for infants, *Acta Paediat Scand, 55*: 273, 1966.
67 Stuart Harris, C. H *I fluenza and other V ru Infect ns of the Resp ratory tract* Ed ard Arnold ltd, London 1965, 2nd ed.
68. S tton, R. N P Respiratory iruses in a res dential nursery *J Hyg (Camb) 60*: 51 1962.
69 Tyrrell, D A. J *Commo Colds and R lat Diseases.* Ed ard Arnold ltd, London 1965.
70 Vargosko, A. J Kim, H W Parrott, R. H Chanock, R. M. Association of Coxsa kie virus with minor respiratory tract illness children *Amer J Dis Ch ld, 104*: 530 1962.
71 V gosko, A. J Kim, H W Parrott R Jeffries, B. C., Wo g, D & Chanock, R. Recovery and identificatio f adeno ir i fections of infant and children, *Bact R* 487 1965.
72 va der Veen, J: The role f denovir respiratory diseases, *Amer Rev Resp Dis* 1963.
73. Wolo tis, S., Tunevall, G & Sterner G irus type 5 infections. An outbreak pharyngitis in home for inf ts, *A Scand 54* 57 196

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 191 1969

CARDIOVASCULAR RESPONSE OF THE NEONATAL LAMB TO HYPOXIA, HYPERCAPNIA AND METABOLIC ACIDOSIS

BY ANTTI KOIVIKKO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

131. Mellbin, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw. kr. 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw. kr. 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr. 25.— 1962
134. Möller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr. 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw. kr. 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr. 25.— 1962
137. Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr. 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr. 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr and Westerberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress, Copenhagen 1961.* Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wasz-Höckert, Ole and Donner, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr. 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr. 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr. 25.— 1963
147. Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Bergen, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr. 20.— 1963
149. Valaes, Tiberi, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr. 25.— 1963
150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization at the X International Congress of Paediatrics, Lisbon, 1962.* Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr.

sm in Newborns. A Clinical and Cytogene-
30.— 1964
piratory Studies in Children. XI. Mechanics
Volumes and Ventilatory Capacity in Asth-
Attack to Symptom-free Status. Sw. kr

ments and his Textbook on Paediatrics. Edi-
and Arvid Wallgren. Sw. kr. 25.— 1964
K. and Ockerman, P. A., Glycogenosis Type
e-6-Phosphatase) in Four Siblings. Sw. kr

Cortisol in the Newborn Infant. Sw. kr. 25.—

159. *Proceedings of the Fourteenth Northern Paediatric Congre*
Stockholm, 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Ockerman, P. A., Glycogen Storage Disease in Sweden. Sw. k
25.— 1965
161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fe
and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation
Health and in Haematological Disease during Childhood. S
kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivat
and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J.
Bronchiectasis: A Review of 187 Cases in Children with Follo
up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheum
toid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Ma
rial of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children, a Longitu
nal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right He
in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death.
Morphological and bacteriological study based on 264 autopsi
Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chotzoudis.* Sw. kr. 15.— 19
173. Walsh, S. Zoe, The Oesophageal Electrocardiogram during t
First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type.
clinical study before and after operation with special refere
to haemodynamic function. Sw. kr. 25.— 1967
175. Hägglund, Pentti, Vectorcardiographic Studies in Newborn I
fants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infectio
Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress, Berge*
1967. Sw. kr. 15.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatric Practice w
Special Regard to Measurements of the Ventricular Size. S
kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edite
by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody R
sponse to *E. Coli* O-Antigens in Infants and Children wi
Urinary Tract Infection, Using Passive Haemagglutinatio
Technique. Sw. kr. 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance in t
Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodologic
and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F., and Sprecher, Howard, A Review of Huma
Placental Lipid Metabolism and Transport. Sw. kr. 25.— 19
184. Robertson, Bengt, The intrapulmonary arterial pattern in norm
infancy and in transposition of the great arteries. Sw. kr. 25.
1968
185. Andersen, Else, Skeletal Maturation of Danish School Childr
in Relation to Height, Sexual Development, and Social Cond
tions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Revi
of the Literature and Report of Nine Cases. Sw. kr. 25.— 19
187. Karlberg, Petter, et al., The Development of Children in a Sw
dish Urban Community. A Prospective Longitudinal Study I–V
Sw. kr. 30.— 1969
188. Mossberg, Gunnar W. and Melin, Kerstin, Studies in Glucos
Galactose Malabsorption. A Clinical Study of 6 Cases and
Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbo
Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of t
Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.
1969
191. Kahiluoto, Antti, Cardiovascular Response of the Neonatal Lam
to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.
1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseas
in Children. Sw. kr. 30.— 1969

Swed. kr. 30.—

by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 191 1969

CARDIOVASCULAR RESPONSE OF THE NEONATAL LAMB TO HYPOXIA, HYPERCAPNIA AND METABOLIC ACIDOSIS

BY ANTTI KOIVIKKO

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

CARDIOVASCULAR RESPONSE OF THE NEONATAL LAMB TO HYPOXIA, HYPERCAPNIA AND METABOLIC ACIDOSIS

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 191 1969

From the Cardiorespiratory Research Unit the Department of Physiology and the Children's Hospital of the University of Turku, Turku, Finland

CARDIOVASCULAR RESPONSE OF THE NEONATAL LAMB TO HYPOXIA, HYPERCAPNIA AND METABOLIC ACIDOSIS

by

Antti Koivikko

TURKU 1969

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 191, 1969

From the Cardiorespiratory Research Unit, the Department of Physiology and the Children's Hospital of the University of Turku, Turku, Finland

CARDIOVASCULAR RESPONSE OF THE NEONATAL LAMB TO HYPOXIA, HYPERCAPNIA AND METABOLIC ACIDOSIS

by

Antti Koivikko

TURKU 1969

Printed in Finland

KIRJAPAINO POLYTYPOS TURKU 1969

CONTENTS

Printed in Finland

Kirjapaino Polytypos Turku 1969

CONTENTS

Symbols and abbreviations

CO	cardiac output	————————
HR	heart rate	O— — — — — — — —O
SV	stroke volume	+ ———————— +
CBV	central blood volume	□— — — — — — — —□
SV/CBV	ratio of SV to CBV	— — — — — — — —
AT	appearance time	— — — — — — x

Introduction

Fetal and newborn mammals tolerate longer periods of asphyxia than adults. This is very appropriate because disorders of oxygen transport from the placenta or lungs to the peripheral tissues develop very easily in fetuses and newborn infants. The reasons for the good asphyxia tolerance of the latter are probably special adjustments of the cellular energy metabolism and the cardiovascular function.

The cardiorespiratory system of a newborn reacts similarly to some stimuli as that of an adult. Important differences exist, however. The pulmonary vascular resistance remains at a higher level in newborn infants than in adults for several postnatal weeks, the fetal shunts open easily in response to hypoxia during the first days after birth and the acid-base values of infants during the first week differ somewhat from the values in adults. The cardiac response to arterial hypoxia is weaker in newborn infants than in adults, and during hypoxia the pulmonary vascular resistance increases comparatively more than later in life. These characteristics of fetal and neonatal mammals, although appropriate before birth, do not always appear so after birth.

In adult mammals the circulation will preferentially supply oxygen to the most important organs during shock and severe asphyxia. This aspect has been little studied in neonatal mammals, but there is evidence that a similar adjustment of the circulation may occur in newborn and also fetal mammals.

The myocardial and brain tissues of newborn mammals may function *for some time* with only anaerobic energy metabolism. This ability is not without limit and therefore physicians have to support the most important functions. The most successful methods of treatment are positive-pressure *ventilation* with oxygen and infusion of alkaline buffers and glucose. Many other methods have been suggested, but in general they have not been successful.

Treatment with oxygen and alkali-glucose infusion are known to improve the prognosis *of asphyxiated infants, but little is known* about the physiological bases of these therapeutical methods. From a clinical standpoint, it is important to know the course of hemodynamics during asphyxia. Furthermore, it would be of value to know the separate effects of hypoxia, hypercapnia and metabolic acidosis. Thus it seemed that these aspects would be worth experimental study. A *preliminary* report of some of the results of hypoxia and hypercapnia experiments with newborn lambs has already been published (72).

Symbols and abbreviations

CO	cardiac output	————————
HR	heart rate	○— — — — — — — —○
SV	stroke volume	+ ————————
CBV	central blood volume	□— — — — — — — —□
SV/CBV	ratio of SV to CBV	— — — — — — — —
AT	appearance time	× — — — — — — ×

TABLE I Flow rates in different parts of the circulation of infants, lambs and calves in different stages of development. All values are given in ml/min kg if not otherwise mentioned.

	Umbilical flow	RV output	LV output	Cardiac output	Method	Ref
					Electromagnetic flowmeter	(7)
Human fetuses 10—28 gest. weeks	100—130					
Newborn infants				540 ml/min 2.5 l/min m²	Dye dilution	(93)
Newborn infants					Dye dilution	(4)
— early clamped		2.11 l/min m²	2.67 l/min m²			
— late clamped		1.02	2.07			
Newborn premature infants					Dye dilution	(123)
— without RD				5.33 l/min m		
— with RD				4.5		
Infants					Estimated	(111)
— 1 year				163		
— 2 year				131		
Fetal lambs					Venous occl.	
— 60—90 gest. day	150—250				plethysmogr	(24)
— at term	125±31					
Fetal lambs					Venous occl.	
— 60 gest day	160				plethysmogr and	(1)
— term	120				flowmeter	
Fetal lambs		Combined				
— 95 gest days		293			Cardiometer	(12)
— at term		240				
Newborn lambs		220			Fick	(25)
Fetal lambs at term		179.7±56.4	181.7±50.6		Dye dilution	(84)
Newborn lambs						
— before ventilation		135	97		Electromagnetic	(9)
— after ventilation		189	164		flowmeter	
Newborn lambs				325±29	Fick	(78)
Neonatal lambs				443	Dye dilution	(117)
Calves						
— neonatal				190		(101)
— at 8 weeks				140		

From data on blood volume and circulation time.

appearance time if the central blood volume per kilogram remained unchanged, but the variation of central blood volume with age is not known.

The circulation time in the newborn infant seems to be only slightly affected by the activity of the infant (118). In adults, the circulation time tends to decrease somewhat during physical exercise (60). The observation that the circulation time does not vary significantly with the site of injection (arm or central vein) (66, 118) supports the view that the circulation time is less dependent on the distance than on the blood volume and flow rate between two sites.

According to Hamilton *et al.* (56) the central blood volume (CBV) is the volume of blood between the venous injection and arterial registration sites. This volume cannot be accurately defined physiologically or anatomically. Hegglin *et al.* (60) reported that it amounts to 25±6 per cent of the total blood volume in the normal adult. This CBV has not been studied in infants or children.

A linear relationship has been found between the

Previous Investigations

BASAL CIRCULATORY VALUES IN THE FETAL AND NEONATAL PERIODS

Tal le I presents previously reported flow rates in diff rent part of the f tal and neonat l irculation. Assali t al (7) recorded umbilical l lood flows of 100 to 110 ml/n in kg in human fetuses. There was no variation in the flow rate with increasing gesta tional ge from 10 to 28 weeks. If the umbilical l lood flow in human f tuses were 05 per cent of the total cardiac output (20) the latt r would be about 150 to 200 ml/min kg

I ree an l Cassels (98) were the first to use the dye dilution method in a tudy of the irculation in new born infants. They obtained a cardiac index of 3.5 l/ in m They also reported that the cardiac output was higher in infants over 15 hours old than in younger infa ts. Recently Arellia et l (4) measured the output of each v ntricle in newborn infants an l ol tained high values for the left ventricular output than I ree and Cassels. The left ventricula output exceeded the right v nt icular out ut The outputs were higher i infants in which th umbilical cord was lamped early than in infa ts i which the cor l was clamp l lat The lower cardiac output i th former group was probably a compensatory phenom enon resulting from polycythemia arising from the low ring of the pla ma volu e which occurs withi a few h urs after l irth in late-cla uped infant (126) The cardia output pe square met r of body rea in newborn inf nts seems t be lose to tl e lower norm al li it in a lults, w ich is taken to l about 3.0 l/ min m (00)

Using a cardi met r D rcroft t al (13) measured coml ined left an l right ventricula outputs of 303 a l 240 l/min kg in f tal lambs on the 06th gest tional day and at t rm respecti ly These results agree w ll with ini olserv ti ns l ilical l lood flow (1 1) whe it is borne i i l that 05 p r cent of the tot l fet l rdia outp t flo t the place ta (29) Electromagneti measure ent f orti an l p lm nary art rial blood flow l y Assali t l (9) l so ga alues f the tot l cardiac output whi h gree with the result of Barcroft t al. However much larger car liac outputs w re measured l y Mahon et l (84) using the l y dilution method.

Th output of the ventricles of the lamb learly increase when respiratio begins, l ut the output of the left ventricle increases more than that of the right ventricle (9) This difference arises immediat ly aft r the lu gs are inflated (9) The measured cardiac outputs of neonatal lambs are divergent Applying the direct Fick principle Cross et al (70) measured a value of 3.3 ml/min kg, whereas St hlman t al (117) ol tained the much high r value 415 ml/min kg using the dye dilution method.

The measure ent of irculati time has been used as a liagnostic tool in liseases i volving hemodynamic hanges, but the time does not alone gi sufficient information o the stat of the circulation. The rece tly used lye dilution method gives much a ldi tional i formation.

Circulation ti es ove diff rent distances ol tained l lifferent methods are shown in Tal le II It will be noted that methods (histamine rash nd fluor escein) based o visual olservation u ually give longer irculatio times than the dye dilution method, i which the sul jectiv rror is small.

The irculati n time from rm to f ce (lip con junctiva or ea) seems t be bout seven seconds in tl newborn inf nt (60) This time lecreases t about four seco l lu ing first th ee weeks ft r birth (60) Thi decrease of the app arance time was l served lso by Lesser t al (77) After th i itial l crease the appearance ti e inc ases with increasi g age and body size t a alue f 0 to 10 seconds in a lult (00)

Th h ge i circulatio ti e from birth t lulthood is small in co parison with the in rease l lood ol The circulati time from rm to lip, f r ple l rel ted t the ratio f the ce tral blood ol me to th cardia utput Th cardi output calculated from the sult f I e l C sels (98) is bout 170 ml/ i kg in ewborn i f t whereas according t H gglin t l (00) th cardia utput is bo t 80 ml ml kg in a lult This lecreased cardia tp t would expla the lo ger

ᴍᴀʙʟᴇ I. Flow rates in different parts of the circulation of infants, lambs and calves in different stages of development. All values are given in ml/min kg if not otherwise mentioned.

	Umbilical flow	RV output	LV output	Cardiac output	Method	Ref.
					Electromagnetic flowmeter	(7)
Human fetuses 10—28 gest. weeks	100—120					
Newborn infants				540 ml/min 2.5 l/min m²	Dye dilution	(95)
Newborn infants					Dye dilution	(4)
— early clamped		2.11 l/min m²	2.27 l/min m²			
— late clamped		1.93	2.07			
Newborn premature infant					Dye dilution	(129)
— without RD				5.53 l/min m²		
— with RD				4.83		
Infants					Estimated	(111)
— 1 year				163		
— 2 year				121		
Fetal lambs						
— 60—90 gest. days	160—250				Venous occl. plethysmogr.	(4)
— at term	128±31					
Fetal lamb					Venous occl. plethysmogr. and flowmeter	(1)
— 80 gest. day	160					
— at term	130					
Fetal lamb		Combined			Cardiometer	(12)
— 93 gest. days		393				
— at term		240				
Newborn lambs		230			Fick	(23)
Fetal lambs at term		179.7±56.4	191.7±30.6		Dye dilution	(84)
Newborn lambs						
— before ventilation		138	97		Electromagnetic flowmeter	(9)
— after ventilation		160	164			
Newborn lambs				283±39	Fick	(26)
Neonatal lambs				433	Dye dilution	(117)
Calves						(101)
— neonatal				190		
— at 8 weeks				140		

From data on blood volume and circulation time.

appearance time of the central blood volume per kilogram remained unchanged, but the variation of central blood volume with age is not known.

The circulation time in the newborn infant seems to be only slightly affected by the activity of the infant (11). In adults, the circulation time tends to decrease somewhat during physical exercise (66). The observation that the circulation time does not vary significantly with the site of injection (arm or central vein) (66, 116) supports the view that the circulation time is less dependent on the distance than on the blood volume and flow rate between the sites.

According to Hamilton *et al.* (36) the central blood volume (CBV) is the volume of blood between the venous injection and arterial registration sites. This *volume cannot be accurately defined physiologically or anatomically*. Hegglin *et al.* (00) reported that it amounts to 38±6 per cent of the total blood volume in a normal adult. This CBV has not been studied in infants or children.

A linear relationship has been found between the

Previous Investigations

BASAL CIRCULATORY VALUES IN THE FETAL AND NEONATAL PERIODS

Table I presents previously reported flow rates in different parts of the fetal and neonatal circulation. Assali t al. (7) recorded umbilical blood flows of 100 to 130 ml/min kg in human fetuses. There was no variation in the flow rate with increasing gesta tional age from 10 to 28 weeks. If the umbilical blood flow in human fetuses were 65 per cent of the total cardiac output (29) the latter would be about 160 to 200 ml/min kg

Prec and Cassels (98) were the first to use the dye dilution method in a study of the circulation in new born infants. They obtained a cardiac index of 2.5 l/min m² They also reported that the cardiac output was higher in infants over 15 hours old than in younger infants. Recently Arcilla et al. (4) measured the output of each ventricle in newborn infants and obtained higher values for the left ventricular outp t than Prec and Cassels. The left entricular output exceeded the right entricular output The outputs were higher in infants in which the umbilical cord was clamped early than in infants in which the cord was clamped late The lower cardiac output in the former group was probably a compensatory phenomenon resulting from polycythemia arising from the lowering of the plasma volume which occurs within a few hours after birth in late-clamped infant (126) The cardiac output per square meter of body area in newborn infant seems to be close to the lower normal limit in adults, which is taken to be about 2.6 l/min m² (60)

Using a cardiom ter Barcroft et l (1) measured combined left and right entricular outputs of 39. nd 40 ml/min kg in fetal lambs on th 95th gestational day a d t t rm, respectively These results agree well with later observations on umbilical blood flow (1 4) when it is borne in mind that 65 per cent of the total f tal cardiac output flow t the placenta (29) Electromagnetic measurements of aortic and pulmonary arterial blood flow by Assali et al. (9) also ga lues of the total cardiac output which agree with the results f Barcroft t al. Howeve much larger cardiac output were measured by Mahon et al. (84) using the dye dilution method.

The outputs of the entricles of the lamb clearly increase when respiration begins, but the output of the left entricle increases more than that of the right entricle (9) This difference arises immediat ly fter the lungs are inflated (9) The measured cardiac outputs of neonatal lambs are diverge t. Applying the direct Fick principle Cross et al. (26) measured a alue of 325 ml/min kg, whereas Stahlman et al. (117) obtained the much higher alue 445 ml/min kg using the d e dilution method.

The measurement of circulation time has been used as a diagnostic tool in diseases in ol ing hemodynamic changes, but the time does not lone gi e sufficient information on the state of the circulation. The recently used dye dilution method gi es much addi tional information.

Circulation times o er different distances obtained by differe t methods are shown in T ble II. It ill be noted that methods (histamine-rash and fluorescein) based on isual bservation usually gi e longer circulation times than the dye dilution method, in which the subjective error is small.

The circulation time from arm to face (lip con junctiva or ear) seems to be about seve seconds in the newborn infant (66) This time decreases to about four seconds during first three eeks after birth (66) This decrease f the ppearance time was observed also by Lesser t al. (77) After the initial decrease, the appearance time i creases with increasing age and body size to a value f 9 to 10 seco ds in an dult (60)

Th hange in circulatio tim from birth to lulthood is small in compariso with the increase in body size The circulation time from arm t lip, for example, is related to the ratio of the central blood volume t the cardia output. The cardiac output calculated from the results of Prec nd Cassels (98) is bout 170 ml/min kg in newborn infants, hereas according t Hegglin et l. (60) the cardia utput is bout 80 ml/min kg in an dult. Thi decreased cardiac output ould xplain the lo ger

begin this review with description of the adult circulation during hypoxia.

In the following the term hypoxia refers to arterial hypoxia unless mentioned otherwise. The term asphyxia refers to all states including hypoxia, hypercapnia and/or metabolic acidosis that result from reduced gas exchange.

Hemodynamic changes

The high-output pattern

Local acute arterial hypoxia induces an increased blood flow by dilating the arterioles in most organs (81). This counteracts the effect of decrease in the oxygen-carrying capacity of the blood. It seems that oxygen deficiency is the regulating factor because neuronal control and increased levels of carbon dioxide, lactic acid and other agents known to cause arteriolar vasodilatation are not necessary for vasodilatation in hypoxia (54). Every vascular bed is, however, under constant neuro-humoral control which may counteract the direct effect of hypoxia. This system is assumed to work via vasodilating β- and γ-receptors and vasoconstricting α-receptors in arterioles. Dermal and renal arterioles do not dilate during hypoxia: this suggests a dominant neuronal vasoconstrictor effect (31). Skin vessels do not exhibit reactive hyperemia, which is seen in the renal vessels. In other tissues, mainly muscle, hypoxia induces pronounced vasodilatation. In cerebral and coronary vascular beds, the lowered partial oxygen pressure is superimposed on other factors having an influence on the state of the arterioles (54).

In most studies where the direct Fick principle has been applied to measure the cardiac output in normal humans (41, 43, 82, 118, 132) in dogs (2, 45, 74, 70, 119) and in sheep (28), increased cardiac output has been observed to result from hypoxia. A consistent increase in blood flow has been found during hypoxia when the dye dilution has been used to estimate the cardiac output in men (38, 43, 44, 4, 107, 120, 122) and calves (78).

Increased cardiac output results from an increase in both the stroke volume and the heart rate in normal man. The stroke volume increases relatively more than the heart rate (39, 41). The heart rate has been stated to increase during hypoxia in the dog but the stroke volume only slightly (69, 120). In contrast, Harrison and Blalock (59) observed only a slight increase in the heart rate and a large increase in the stroke volume in dogs.

The mean arterial pressure varies only slightly in man during hypoxia (39, 132). This reflects the effect of the peripheral vasodilatation. Some variation in the mean arterial pressure is seen in hypoxia in the dog (2, 69).

The central blood volume does not change during hypoxia in man (38, 43). Measurements of central blood volume in anaesthetized dogs have shown that an increase occurs (11, 61, 67, 107, 120). A large increase occurs also in the pulmonary blood volume in unanaesthetized dogs during hypoxia (69).

All reports seen by the author suggest that the circulation time decreases during hypoxia. Both the arm-to-ear and lung-to-ear appearance times decrease clearly during hypoxia in normal adults (13). A decrease in the mean transit time has been measured by the dye dilution method in men (from 12.3 to 10.7 sec.) (43) and in unanaesthetized dogs (from 7.8 to 6.1 sec.) (69) during hypoxia.

The low-output pattern

A different cardiovascular pattern develops in diving animals during diving, i.e. under severe asphyctic conditions, and in rabbits in severe arterial hypoxia. In seal, man and dog the heart rate falls immediately and large regions of the circulation are practically closed (40, 105). The renal blood flow almost stops in the seal and the blood flows through the abdominal aorta, kidney and mesenterium are greatly reduced in the dog during submersion (40). The carotid arterial blood flow of the diving seal decreases considerably but remains higher than any other peripheral flow rate (40). In the submerged greyhound the coronary blood flow remains unchanged (40). Bradycardia during diving can be prevented by atropine which does not influence the peripheral vasoconstriction. The diving pattern can be completely prevented by barbiturate anaesthesia (40).

The completeness of the peripheral vasoconstriction during diving is apparent from the observation that the lactic acid concentration of the peripheral blood increases only very little during the dive but increases immediately after surfacing when the peripheral circulation is opened again (108). In addition to the cardiovascular changes there must occur a reduction of the metabolic rate because the excess oxygen uptake of seals and other diving animals after the submersion period does not correspond to the calculated basal oxygen requirement during the submersion period (108). The basic reason for this lowered oxygen consumption is not known.

Although the high-output pattern may result if rabbits are made moderately hypoxic, a low-output pattern in which the cardiac output decreases abruptly for a few minutes occurs during severe hypoxia in

TABLE II Indicator appearance times (in seconds) over different distances in mammals as determined by different methods.

	Hand to face lip or ear	Umbil. vein to li1 r ear	Pulmonary transit time	Method	Ref
Human beings					
1 t day	7 0			Dye dilution	(66)
3rd week	4.3				
< 5 days	10._			Fluorescein	(77)
1—4 days	7.8			Fluorescein	(93)
*—12 months	10 0				
< 1 year	14.6			Histamine rash	(111)
< years	7.0			Fluorescein	(136)
3—13 years	11.5				
< years	6.5			Fluorescein	(46)
adult	9—10			Dye dilution	(60)
newborn		4.8		Fluorescein	(116)
1st day		3._		Dye dilution	(93)
newborn			1.85	D e dilution	(14)
Newborn lambs					
— before ventil.			.9—4 7	X ray contrast	(5)
— after ventil.			1.0—_7		
Newborn dogs			1.0	X ray contrast	(5_)
Newborn pigs			0.8—1.3		(53)

stroke volume and the CBV (56) This relationship is maintained when the position is changed and luring anesthesia (68) Hegglin t al (60) give a alue of 0.048±0.00. fo the ratio of stroke volume to CBV in a normal adult

CARDIOVASCULAR ADJUSTMENTS IN ACUTE ARTERIAL HYPOXIA

Oxygen seems to be th substance whose transport is most depe dent on dequate peripheral blood flow Guyton (54) states that the safety factor for oxygen transport is only threefol l, wh reas this fact is onsiderabl larger fo othe nutrient wastes _3-f ld for carbo dioxide 23 fold for fatty a i ls, 30-fold for glucose, 30-fold for mino acids, and 450-f ld for nit ogenous wastes. It is also known that a decrease i cardia output by one third causes hypoxia in most tissues, wh reas a decrease of this magnit de does not reduce the o erall transport of other subst aces. A decreased xygen transport to itoch ndria ma result from a low ambient partial pressure of o gen, ins ffic ent gas exchang in the lungs, severe anemia methemoglol inemia, carbon mo xid and yanide poi-oning, nd physical ffort The cardiovascula djustments seen t be roughly the same i t rial hypoxia a d physical ercise (54)

Most f ou knowledge f the irculatory hanges during hypo ia is based on xperiment l lat for ad lt mammals. The f re it are ed ppropriate to

begin this review with description of the adult circulation during hypoxia.

In the following the term hypoxia refers to arterial hypoxia unless mentioned otherwise. The term asphyxia refers to all states including hypoxia, hypercapnia and/or metabolic acidosis that result from a reduced gas exchange.

Hemodynamic changes

The high-output pattern

Local acute arterial hypoxia induces an increased blood flow by dilating the arterioles in most organs (63). This counteracts the effect of the decrease in the oxygen-carrying capacity of the blood. It seems that oxygen deficiency is the regulating factor because neuronal control and increased levels of carbon dioxide, lactic acid and other agents known to cause arteriolar vasodilatation are not necessary for vasodilatation in hypoxia (64). Every vascular bed is, however, under constant neuro-humoral control which may counteract the direct effect of hypoxia. This system is assumed to work via vasodilating β-adrenoreceptors and vasoconstricting α-receptors in arterioles. Dermal and renal arterioles do not dilate during hypoxia; this suggests a dominant neuronal vasoconstrictor effect (31). Skin vessels do not exhibit reactive hyperemia, which is seen in the renal vessels. In other tissues, mainly muscle, hypoxia induces pronounced vasodilatation. In cerebral and coronary vascular beds, the lowered partial oxygen pressure is superimposed on all other factors having an influence on the state of the arterioles (31).

In most studies where the direct Fick principle has been applied to measure the cardiac output in normal humans (41, 53, 67, 118, 122), in dogs (3, 44, 56, 99, 119) and in sheep (26) an increased cardiac output has been observed to result from hypoxia. A consistent increase in blood flow has been found during hypoxia when the dye dilution has been used to estimate the cardiac output in men (33, 43, 44, 45, 107, 120, 122) and others (78).

Increased cardiac output results from an increase in both the stroke volume and the heart rate in normal man. The stroke volume increases relatively more than the heart rate (35, 41). The heart rate has been found to increase during hypoxia in the dog but the stroke volume only slightly (60, 120). In contrast Harrison and Blalock (34) observed only a slight increase in the heart rate and a large increase in the stroke volume in dogs.

The mean arterial pressure varies only slightly in man during hypoxia (23, 122). This reflects the effect of the peripheral vasodilatation. Some variation in the mean arterial pressure is seen in hypoxia in the dog (3, 89).

The central blood volume does not change during hypoxia in man (34, 43). Measurements of central blood volume in anesthetized dogs have shown that an increase occurs (11, 61, 67, 107, 120). A large increase occurs also in the pulmonary blood volume in unanesthetized dogs during hypoxia (69).

All reports seen by the author suggest that the circulation time decreases during hypoxia. Both the arm-to-ear and lung-to-ear appearance times decrease clearly during hypoxia in normal adult (13). A decrease in the mean transit time has been measured by the dye dilution method in men (from 12.3 to 10.7 sec.) (43) and in unanesthetized dogs (from 7.6 to 6.1 sec.) (69) during hypoxia.

The low-output pattern

A different cardiovascular pattern develops in diving animals during a dive, or under severe asphyctic conditions, and in rabbits in severe arterial hypoxia. In seal, man and dog the heart rate falls immediately and large regions of the circulation are practically closed (40, 103). The renal blood flow almost stops in the seal and the blood flows through the abdominal aorta, kidneys and mesenterium are greatly reduced in the dog during submersion (40). The carotid arterial blood flow of the diving seal decreases considerably but remains higher than any other peripheral flow rate (40). In the submerged greyhound the coronary blood flow remains unchanged (40). Bradycardia during diving can be prevented by atropine which does not influence the peripheral vasoconstriction. The diving pattern can be completely prevented by barbiturate anesthesia (40).

The completeness of the peripheral vasoconstriction during a dive is apparent from the observation that the lactic acid concentration of the peripheral blood increases only a little during the dive but increases immediately after surfacing when the peripheral circulation is opened again (103). In addition to the cardiovascular changes there must occur a reduction of the metabolic rate because the excess oxygen uptake of seals and other diving animals after the submersion period does not correspond to the calculated basal oxygen requirement during the submersion period (103). The basic reason for this lowered oxygen consumption is not known.

Although the high-output pattern may result if rabbits are made moderately hypoxic, a low-output pattern in which the cardiac output decreases abruptly for a few minutes occurs during severe hypoxia in

TABLE II Indicator appearance times (in seconds) over different distances in mammals as determined by different methods.

	Hand to face, lip or ear	Umbil. vein to lip or ear	Pulmonary transit time	Method	Ref.
Human beings					
1st day	7.0			Dye dilution	(66)
3rd week	4.3				
< 5 days	10.2			Fluorescein	(77)
1—42 days	7.8			Fluorescein	(93)
2—12 months	10.0				
< 1 year	14.9			Histamine rash	(111)
< 2 years	7.0			Fluorescein	(136)
3—13 years	11.5				
< 3 years	6.5			Fl orescein	(46)
adult	9—10			Dye dilution	(60)
newborn		4.8		Fluorescein	(116)
1st day		3.8		Dye dilution	(93)
newborn			1.85	Dye dilution	(14)
Newborn lambs					
— before ventil.			2.9—4.7	X ray co trast	(5)
— after ventil.			1.0—2.7		
Newborn dogs			1.0	X ray co trast	(52)
Newborn pigs			0.8—1.2		(52)

stroke olume and the CBV (56) This relationship is maintained when the positio is ha ged an l luring a esthesia (68) Hegglin t al (60) gi e a alue of 0.048 ± 0.005 fo the ratio of stroke olume to CBV in normal adult

CARDIOVASCULAR ADJUSTMENTS IN ACUTE ARTERIAL HYPOXIA

Oxygen seems t be the substance whose transport is most dependent o dequate peripheral blood flow Guyton (54) states that the saf ty f tor f oxyge transport is only threef ld, whereas this f cto is considerabl larger fo ther n trients o wastes 23-f ld for carbon dioxide 28-fold for fatty cids, 30-fold for glucose, 36-fold for amino acids, and 480-fol l fo nitrogenous wastes. It is also known that decrease in cardiac output by ne third causes hypoxia in most tissues, whe eas a decrease f this magnitud does not reduce the rall transport f ther substances. A decreased oxygen transport to mitoch dria ma result from a low ambient partial pressure f oxygen, insufficie t gas exchang in the lungs, severe anemia, methemoglol inemia, carbon monoxide d cyanide poisoning, a d physical effort The cardiovascular djustment seem t be roughly th same in rt rial hypoxia d physical ise (54)

Most of ur knowledge f the irculatory ha ges luring hypoxia is based on perime tal dat fo adult mammals. Theref re it seemed pp ropriate to

gin this review with description of the adult rculation during hypoxia.

I the following the term hypoxia refers t arterial poxia unless mentioned otherwise. The term asphyxia fers to all states including hypoxia, hypercapnia nd metabolic acidosis that result from reduced as exchange

Hemodynamic changes

Th high-output pattern

Local acut arterial hypoxia induces an increased blood flow by dilating the arterioles i most organs 63) This counteract the ffect of decrease in the oxygen-carrying capacity f the blood. It seems that oxygen deficiency is the regulating factor because neuronal control and increased levels of carbon dioxide, lactic acid and other gents know to cause arteriolar asodilatation are not necessary for asodilatation in hypoxia (34) E ery ascular bed is, however under constant neuro-humoral control hich ma counteract the direct ffect f hypoxia. This system is assumed ork as asodilating β nd γ receptors and asoconstricting receptors in arterioles. Dermal and renal arterioles do not dilate during hypoxia; this suggests dominant neuronal vasoconstrictor effect 31) Skin cscle do not exhibit reactiv hyperemia, hich is seen in the renal ssels. I other tissues, mainly muscle, hypoxia induces pronounced sodilatation In cerebral and coronary vascular beds, he lowered partial oxygen pressure is superimposed on all other factors ha ing an influence on the stat f he arterioles 54)

I most studies here the direct Fick principle has been pplied to measure the cardiac output in normal humans 41 53, 83, 118, 142) in dogs (3, 48, 58, 70, 119 and in sheep (26) an increased cardiac output has been observed t result from hypoxia A consistent increase in blood flow has been found during h poxia when the dy dilution has been used estima the cardia output in men (38, 43, 44, 45, 107 120, 122) and calves (78

Increased cardiac output results from an increase in both the stroke olume and the heart rat in normal man The stroke olume increases relatively more han the heart rate (38, 41) The heart rate ha been stated increase during hypoxia in the dog but the stroke olume onl slightly (68, 120) I contrast, Harrison and Blalock (58) observed onl slight increase in the heart rate and large increase in the stroke olume in dogs.

The mean arterial pressur varies only slightly in man during h poxia (38, 122) This reflects the effect f the peripheral asodilatation. Some ariation in the mean arterial pressure is seen in hypoxia in the dog (3, 69)

The central blood olume does not change during hypoxia in man (38, 43) Measurements f central blood olume in anesthetized dogs have show that an increase occurs (11 41 67 107 120) A large increase occurs also in the pulmonary blood olume in unanesthetized dogs during hypoxia (69)

All reports seen by the uthor suggest that the circulation time decreases during hypoxia. Both the arm-to-ear and lung to-ear ppearance times decrease learly during hypoxia in normal adult (13) A decrease in the mean transit time has been measured by the d dilution method in men (from 12.3 to 10.7 sec.) (43) and in unanesthetized dogs (from .8 t 6.1 sec.) (69) during hypoxia.

The low-output pattern

A different cardiovascular pattern develops in diving animals during div g under severe asphyctic conditions, and in rabbits in severe arterial hypoxia. In seal, man and dog the heart rate falls immediately and large regions f the circulation are practically closed (40, 105) The renal blood flow almost stops in the seal and the blood flow through the abdominal aorta, kidney and mesenterium are greatly reduced in the dog during submersion (40) The carotid arterial blood flow f the diving seal decreases considerably but remains higher than any other peripheral flow rate (40) In the submerged greyhound the coronary blood flow remains unchanged (40) Bradycardia during diving can be prevented by atropine which does not influence the peripheral vasoconstriction. The diving pattern can be completely prevented by barbiturat anesthesia (40)

The completeness f the peripheral vasoconstriction during div g is apparent from the observation that the lactic acid concentration f the peripheral blood increases only little during the d but increases immediately after surfacing hen the peripheral circulation is opened gain (105) I ddition to the cardiovascular changes there must occur reduction of the metabolic rate because the excess oxygen uptake f seals nd other diving animals after the submersion period does not correspond t the calculated basal oxygen requirement during the submersion period (106) The basic reason for this lowered oxygen consumption is not known.

Although the high-output pattern may result if rabbit are made moderately hypoxic, low-output pattern in which the cardiac output decreases abruptly for few minutes occurs during severe hypoxia in

rabbits ($pO_2 < 35$ mmHg). The arterial pressure increases gradually and there is pronounced bradycardia (74). The peripheral pressor response is mediated via sympathetic α receptors and this response may be prevented by administration of dibenzyline (74). During this kind of cardiovascular response oxygen uptake is low. The uptake returns to normal when air breathing is resumed. This pattern may also occur in dogs during hypoxia if the arterial oxygen *partial pressure* decreases to that observed in rabbits (less than 35 mmHg) (74).

Regulation of cardiovascular function during hypoxia

The peripheral demand for increased cardiac output during moderate hypoxia is evidently well satisfied. This is apparently due mainly to peripheral vasodilatation and autonomic heart function and is evident from experimental data which show that inhibition or destruction of large parts of the assumed regulation system does not seriously affect the response to hypoxia.

Already the studies of Harrison *et al.* (50) who used a technique based on the Fick principle indicated that vagotomy, administration of atropine, thoracic sympathectomy, ligation of both carotid and subclavian arteries and bilateral adrenalectomy, individually or in different combinations, did not significantly change the hypoxic increase of the cardiac output in the dog. Gömöri *et al.* (48) also observed a normal response of the cardiac output to hypoxia after bilateral adrenalectomy, no response during isolated cerebral hypoxia and a normal response during isolated trunk hypoxia (the brain being perfused with oxygenated blood).

More detailed studies have indicated the existence of neuro-humoral regulation during hypoxia. Downing *et al.* (34) showed that isolated cerebral ischemia in the dog increased the heart rate, peripheral resistance and myocardial contractility. Cessation of sympathetic activity of the central nervous system following the occlusion of the brain blood arteries ... was followed by decreased myocardial contractility during hypoxia (36). Ablation of the sympathetic chain from C 3 ... Th 8 in conscious dogs reduced the increase in cardiac output during moderate hypoxia (90). Richardson *et al.* (103) observed that beta-adrenergic blockade in man did not significantly reduced the increase in heart rate and cardiac output caused by hypoxia. β-adrenergic blockade in rabbits weakens the cardiac output response to hypoxia (74). Reserpine seems to have a similar effect on the heart, agents effecting beta blockade (123). On the other hand, *depletion of the peripheral stores of norepinephrine by syrosingopine* did not change the cardiovascular response to mild hypoxia (81). *The importance of a proper nervous regulation during maximal physical exertion was demonstrated by Donald et al.* (32) who observed that the racing performance of greyhounds was lower after heart denervation and/or beta-adrenergic blockade.

In contrast to the evident influence of the central sympathetic system on the functions of the heart and peripheral vessels, the influence of peripheral chemoreceptors on the hypoxic circulatory regulation has been found to be of minor importance (33, 31, 9).

The type of respiratory response seems to play some part in cardiovascular regulation. Korner (74) concluded that large-lunged men and dogs with a good respiratory response to hypoxia develop the high-output pattern and small-lunged rabbits the low-output pattern. He assumes that the arterial oxygen pressure is the factor determining the type of cardiovascular response.

Strong central nervous participation is suggested by experimental data for seals which develop the low-output pattern during a normal dive but when they "know" that they can breathe through a mouthpiece any time they wish, this pattern will not occur (108). Primary central nervous regulation has also been observed during exercise: the stroke output of the heart increases at the moment when a dog begins to run without any chemical changes occurring in the blood (100).

The above may be summarized by stating that increased tissue perfusion develops in adult mammals subjected to moderate low oxygen pressures. This change is controlled mainly by local autoregulation in different tissues and the heart. Neuro-humoral regulation provides a more appropriate distribution of blood flow and oxygen transport in the circulation in severe hypoxia. The peculiar diving pattern may be considered an expression of strong neuro-humoral circulatory control in extreme hypoxic or asphyctic conditions.

Hypoxia in the fetal and neonatal periods

It is obvious that newborn infants and animals are well adapted to meet the demands of extrauterine life. The effect of arterial hypoxia ... the only ... of the neonatal period is not as complicated than later in life because of the high tolerance of hypoxia or asphyxia and the absence of ... ... are not ... well elucidated.

Tol rance of hypoxia

A distinctive characteristic of fetuses and newborn mammals is their tolerance of asphyxia. The nature of this phenomenon is not exactly known. It as arlier thought t be due t a lowered oxygen consumption during hypoxia in both infants (23) and lambs (1 26). However this decrease as later found t be due t the fact that the cool environment had increased the oxygen consumption hich decreased normal alone again during hypoxia (84). This decreased oxygen consumption during hypoxia does not seem t be restricted t the neonatal period, since it has been found to occur also in dult dogs (89).

Newborn mammals develop signs of oxygen debt during hypoxia. I newborn lambs the lactic acid concentration increases up to 52 mg per 100 ml during hypoxia (26). The lactic acid concentration f premature infants increases during physical activity and returns to normal afterwards, but more slowly than in adults (50). In the respiratory distress syndrome the lactic acid concentration may rise up to 11 mM, and is negatively correlated ith the decreasing arterial oxygen pressure (129). Infants suffering from the respiratory distress syndrome ha e reduced oxygen uptake. During recovery this ptake increases first to level bel normal and then become normal again (79). Similarly the oxygen uptake seems t be high t first during positive-pressure entilation for the resuscitation f asphyx iated infants, but falls to ithin normal limits during recovery (31).

There is no information ailable that ould show hether newborn mammals ea oxygen in h poxic or asph tic conditions. As mentioned above, such a ing occurs in seals during div (106).

The factors determining the tolerance of hypoxia i adults and possibly also fetuses and newborns are the capacities f the central nervous ystem and the heart. Oxygen deficiency seems t be the factor hich limit he function f hese organs rather than increased arbon dioxide levels. When subjected to pure oxygen ten, adult dogs lived 85 minutes ith final partial carbon dioxide pressure of nearly 400 mmHg and blood pH f 6.5 t 6.6, but dogs breathing pure nitrogen surv ed only 9 minutes (73).

I complet asphyxia resulting from an occluded ather, the m ocardial gly ogen f rabbits decreases in 3 minutes t minimum alue that is less than 10 per ent of the normal level (62). I this stat he myocardium f the dog is no longer able to use blood glucose (47. The possibilities of anaerobic energy metabolism seem t be better in newborn ra les ce its myocardium has much larger glycogen store and higher phosphorylase content than an adult rat heart (133). The anaerobic glycolytic activity appears t be nearly sufficient to satisfy the lower energy requirement f the brain f the newborn (39).

From the clinical standpoint it would be important if newborn could be kept in state in hich its energy demands are provided by aerobic pathway and energy is not taken from anaerobic sources which deplete glycogen stores.

Cardiovascular reactions

Many stimuli produce cardiovascular response that indicates high degree of maturity in the newborn infant. W llgren *et al.* (127) found that cardiac output and stroke olume decrease and the heart rat and peripheral ascular resistance increase in response t hypervolemia. In addition, signs f rapid hange towards normalization f the blood olume are observed. Also hypervolemia induced by lat cord clamping is corrected in few hours (128). Further more mature response f the arterial blood pressure t body tilting is observed from the fourth day after birth in normal newborn infants (43) whereas such response is not observed in premature infants (37).

The pulmonary ascular resistance increases and the arterial duct tends t reopen in neonatal lambs in arterial hypoxia (96). The same phenomena occur in newborn infants and f the aortic pressure decreases, part of the pulmonary blood flow may be directed t the aorta through the aortic duct (64). This kind of rearrangement f the circulation in severe respiratory distress has been called pulmonary hypoperfusion (22). Such change in the circulation reduces the uptake of oxygen in the lung capillaries. Onl adequate entilation and pulmonary blood flow can break this icious circle.

The heart rates increase by 16 per cent in three minutes hen infants less than six days old are subjected t an inspired oxygen content of 12 per cent (16). Short periods of hypoxia reduce the mean arterial pressure in newborn infants (64). This observation, hich suggests peripheral asodilatation, was confirmed by Celander and Mårild (19) who found that strong reacti hyperemia followed the occlusion f foot and calf blood flow.

Hypoxia in neonatal lamb leads t slight reduction f the left entricular contractility (27) peripheral asodilatation (117) and, in most cases, an levated heart rat (26, 72). The data on cardiac output in hypoxic lambs differ somewhat. Cross *et al.* (26) did not find significant changes in this parameter; slight increase occurred in only four f ten animals. Similar results were obtained with an

rabbits ($pO_2 < 35$ mmHg). The arterial pressure increases gradually and there is pronounced bradycardia (74). The peripheral presso response is mediated via sympathetic α-receptors and this response may be prevented by administration of dibenzyline (74). During this kind of cardiovascular response oxygen uptake is low. The uptake returns to normal when air breathing is resumed. This pattern may also occur in dogs during hypoxia if the arterial oxygen partial pressure decreases to that observed in rabbits (less than 35 mmHg) (4).

Regulation of cardiovascular function during hypoxia

The peripheral demand for increased cardiac output duri g moderate hypoxia is evidently well satisfied. This is apparently due mainly to peripheral vasodilatation and autonomic heart function and is evident from experimental data which show that inhibition or destruction of large parts of the assumed regulation syste does not serious ffect the response to hypoxia.

Already the studies of Harrison *et al.* (59) who used technique based on the Fick principle indicated that vagotomy administration of atropine thoracic sympathectomy ligation of both carotid and subclavian arteries and bilateral adrenalectomy individually o in different combinations, did not significantly change the hypoxic increase of the cardiac output in the dog. Gömöri *et al.* (48) also observed a normal response of the cardiac output to hypoxia after bilateral adrenalectomy no response during isolated cerebral hypoxia and a normal response during isolated trunk hypoxia (the brain being perfused with oxygenated blood).

More detailed studies have indicated the existence of neuro-humoral regulation duri g hypoxia. Dow i g *et al.* (34) showed that isolated cerebral ischemia in the dog increased the heart rat peripheral resistance and myocardial contractility. Cessation of sympathetic activity of the central nervous system following the occlusion of the brachiocephalic arteries in the cat was followed by decreased myocardial contractility during hypoxia (36). Ablatio of th sympath tic chain from C3 to Th8 i conscious dogs reduced th increase in cardiac output during moderate hypoxia (90). Richardson *et al.* (103) observed that beta-adrenergic blockade in man definitely reduced the increase in heart rate and cardiac output caused by hypoxia. β-adrenergic blockade in rabbit weakens the cardia output response to hypoxia (74). Reserpi seems to have a simila ffect th heart s agents effecting beta blockade (1, 3). On the other hand, depletion of the peripheral stores of epinephrine by syrosingopine did not change the cardiovascular response to mild hypoxia (21). The importance of a proper nervous regulation during maximal physical exertion was demonstrated by Donald *et al.* (32) who observed that the racing performance of greyhounds was lower after heart denervatio and/or beta-adrenergic blockade.

In contrast to the evident influence of the central sympathetic system on the functions of the heart and peripheral vessels, the influence of peripheral chemoreceptors on the hypoxic circulatory regulation has been found to be of minor importance (33, 34, 97).

The type of respiratory response seems to play some part in cardiovascular regulation. K rner (74) concluded that large-lunged men and dogs with a good respiratory response to hypoxia develop the high-output pattern and small-lunged rabbit the low output pattern. He assumes that the arterial oxygen pressure is the factor determini g the type of cardiovascular response.

Strong central nervous participation is suggested by experimental data for seals which develop the low-output patt rn during a normal di e but when they know that they can breath through a mouthpiece a y time they wish, thi pattern will not occur (108). Primary central nervous regulation has also been observed during exercise the stroke output of the heart increases t the moment when a dog begins to run without a y chemical changes occurri g in the blood (106).

The above may be summarized by stating that increased tissue perfusio develops i adult mammal subjected to moderately low oxygen pressures. This change is controlled mainly by local at regulatio in different tissues and the heart. Neuro humoral regulation provides a more appropriat distribution of blood flow and oxygen transport i the irculation in severe hypoxia. The peculia di ing pattern ma be considered a expression of stro g euro humoral circulatory control in extreme hypoxic or asphyctic co ditions.

Hypoxia in the fetal and neonatal periods

It f ol lows that newborn inf t d lambs are w ll adjusted t meet the demands f xtra t rine lif . Th ffect f arterial hypoxia o hemodynamics i the neonatal period i m re complicated tha lat in life because f the high tolerance f hypoxia a phyxia nd the existence f fetal shunt that re patent or can be tivated.

on the heart; when heart failure was induced by increasing the pCO_2 in a denervated heart-lung preparation, the cardiac function returned to normal on infusion of epinephrine or norepinephrine. Acetyl strophanthidin also restored the cardiac function. The depressant effect of carbon dioxide on the heart in an intact organism is opposed by sympathetic discharge stimulated by direct cerebral hypercapnia. Isolated cerebral hypercapnia produces increased myocardial contractility, tachycardia and peripheral vasoconstriction (34). On the other hand, beta adrenergic blockade was not found by Wendling et al. (131) to prevent the increase of cardiac output during hypercapnia. Carbon dioxide may depress myocardial function by inhibiting the citric acid cycle and by reducing the oxygen supply by way of the Bohr shift.

The data on cardiac output during hypercapnia are contradictory. According to most reports, the cardiac output increases in man (6, 42, 82, 102, 104) and dog (18). In contrast, Auld et al. (10) did not find any changes in cardiac output, heart rate or peripheral resistance in anesthetized children during hypercapnia. Sunturnen (121) observed both increased, decreased and unchanged cardiac outputs in hypercapnic dogs.

The hyperventilation that occurs at increased carbon dioxide levels may change the cardiac output response because hyperventilation may increase cardiac output even in hypocapnia (82, 104).

Carbon dioxide usually increases the heart rate in man (102), but may cause bradycardia in the dog (92, 1 1). This may be a direct effect on the heart, because Downing et al. (34) found that isolated hypercapnia of the central nervous system of the dog results in tachycardia.

Arterial pressure increases slightly during hypercapnia. This is due to an increased cardiac output in spite of peripheral vasodilatation. Hypotension that often occurs after experimental hypercapnia (110) is most pronounced after the arterial pCO_2 has exceeded 80 mmHg.

Tolerance of a high pCO_2 seems to be good in dogs provided that oxygenation is sufficient. Yahav et al. (91) observed an increase in cardiac output (64 per cent) and a marked bradycardia (28 per cent decrease) after 15 minutes of apneic oxygenation (a pCO_2 of 120 mmHg). The survival time in these conditions may be as long as 63 minutes in dogs with a pCO_2 of nearly 400 mmHg and a blood pH of 6.5 (6).

Conduction disturbances, extrasystoles, bigeminy, abnormal atrial and nodal activity (1) and even ventricular fibrillation (17) have been observed in man during hypercapnia. The disturbances have been attributed to increased serum potassium concentration (70), but this explanation has not been generally accepted (89).

Hypercapnia during the fetal and neonatal periods

Intrauterine asphyxia consists partly of hypercapnia. The influence of isolated hypercapnia in human fetuses has not been investigated. Assali *et al.* (9) ventilated pregnant ewes with carbon dioxide and *found* that the arterial pCO_2 increased, the arterial blood pressure rose and the carotid, femoral and umbilical blood flow increased in the fetuses. These changes possibly indicate an increased cardiac output.

Increased cardiac output has been observed in neonatal lambs during hypercapnia; also the heart rate and central blood volume are elevated (72, 117). Hypercapnia does not, however, alter the state of the arterial duct (96).

EFFECTS OF METABOLIC ACIDOSIS ON THE BLOOD CIRCULATION

The cardiac output is low in dogs suffering from metabolic acidosis (18, 40), but Bekerth (104) and Richardson *et al.* (102) did not find changes in cardiac output in men after infusion of small amounts of lactic or hydrochloric acid. Richardson *et al.* observed an increased cardiac output in men after the infusion of sodium bicarbonate.

A decreased cardiac output has been attributed to decreased myocardial contractility in dogs suffering from metabolic acidosis (27). The heart function slows down less in intact animals than in isolated hearts (40, 93). However, metabolic acidosis does not significantly alter the ventricular function in full-grown cats (24) and newborn lambs (37) after extensive surgery.

The greater ability of an intact organism to withstand a low pH is thought to be due to the function of the sympathetic nervous system. However, Downing *et al.* (36) observed an increased ventricular function when the cerebral blood supply was interrupted. They concluded that lower sympathetic centers begin to function. This view is substantiated by the *observation* that lactic acid infusion usually produces tachycardia and increased arterial pressure corresponding to that produced by the injection of 2 μg/kg of epinephrine; these responses are no longer obtained after the removal of the adrenals (127).

Acidosis may suppress myocardial function by diminishing carbohydrate uptake (40, 93) or may lower the oxygen supply to the myocardium

lectromagnetic flowmeter for newborn calves with normal acid base balance (103) a l fo neonatal lambs with norm al acid base balance when the dye dilution method was used (11) In contrast the preliminary results of Koi ikko (7) show that cardiac output increases during moderate hypoxia in neonat l lambs when acid base conditions are normal.

The central blood v lume increases in neonatal lambs during hypo ia according to preliminary results of Koivikko ( ) More recently Stahlman et al (117) measured pulmonary blood volumes by the slope m thod and reported decreased v lues during hypoxia.

There are data which indicat that the living pattern may occur also in f tuses and newborn infants. Brad cardia which may be due to brain compression nd reduced cerebral blood flow is bserved in human fetuses duri g ut rine co tra tio s (8) Bradycardia continues lo ge than the ut rine co traction period in sphyxiated f tuses. This bradycardia may be prevented with atropine (87) Also the diving bradycardia of seals is prev ted by this drug (40) The la tic acid concentration of the blood of human infants remains low during delivery but increases imm diately aft rwards (65, 1) This variation of the la tic cid co c tration during and fter delivery may reflect peripheral asoconstriction similar to that observed i diving animals. According to Celander (70) breathing f gas mi tures co taini g less than 13 pe cent ox gen produces a decreased blood flow in the limbs and ta h cardia t th same time in infant but then, for a whil pronounced bradycardia. This kind of adjustme t f the peripheral circulation requires a mnt re centrally co trolled vasoconstriction. Already at this age the peripheral vascular bed contract on infusion of norepinephrine (69)

Hypoxia or asphyxia in fetal lambs at term leads to increased rt rial pressure brad cardia, and decreased femoral arterial nd increased carotid and umbilical arterial blood flows (8) Elsner et al (40) observ d a di ing pattern i neonat l calves, but not before the 10th day f life

Effects of acid base changes on the response to hypoxia

The cardiac output f newborn calves decrease in h poxia wh n th animal ha m taboli idosis. The output rev rt to normal when the acid base abnormality nd h poxemia re corrected (103) Similar result were obtained b Ko ikko ( ) for n wborn lambs. As found by Dow ing t l in cat (36) and newborn lambs (37) the decrease seems to be due to decreased myocardial co tractility in these conditions. In the experiment of Downing et al hypoxia or acido is alone did not depress the myocardial contractility significantly but the combined ffect of these conditions was a markedly depressed v ntricular function. This depression was less in newborn lambs than in lult cats, which possibly indicates a better anaerobic capacity in the former

The reason for the decreased myocardial contractility is not clear The factors maintaining the contractility re an adequate supply of oxygen and glucose fo the energy metabolism of the heart and proper function of the sympathetic nervous s stem. In acidosis, in respiratory as w ll in metabolic the Bohr shift may decrease th m ocardial ox gen supply In severe asphyxia the myocardial glycogen stores may be deplet l ntirely and the ability t utilize blood glucose ma be reduced (4) The central nervous systems has a certain regulatory effect on th myocardial co tra tility According to Downi g t al (36) occlusion f the cerebral blood flow during hypoxia associated with metabolic acidosis causes a further decrease in myocardial contractilit

CARDIOVASCULAR ADJUSTMENTS DURING ACUTE HYPERCAPNIA

Hypercapnia in adults

Carbon dioxide removal is not impaired by a moderat decrease in cardia output (34) This may be explained by an effective tra sport of carbon dioxide t the lungs. In sp t of th small pot ntial danger of carbo dioxide retention, the carbon dioxide lev l seems to be ery strong regulator f both local a d central circulation. The quick hanges in e tilation and circulation see in hypercapnia t nd to normalize the a id base conditions. The main sites where carbon dioxide xert it ffects e the rt rioles, the heart the adrenals, a l the chemoreceptors of the aorta, carotid sinus d brain.

Carbon dioxide generally induces dilatation of the arterioles. This effect is particularly stro g in the cerebral irculation, but seems to be weaker i the coronary circulation (106)

Carbon dioxide has a depressant effect on an isolated heart (99) Bo iface and Bro n (15) bserved that entilatio of 3 t 50 per cent ca bon dioxide b p beat dogs resulted i a 13 t 50 per ce t decrease in the tricula co tractile f ce The response to carbo di xide has ften been bserved t be the rev rse after less ext nsi surgery A demonst ted l has nd Ca ert (9) the reason f this seems t be increased sympatheti tion

on the heart; hen heart failure was induced by increasing the pCO_2 in denervated heart-lung preparation, the cardiac function returned to normal on infusion of epinephrine or norepinephrine. Acetyl strophanthidin also restored the cardiac function. The depressant ffect f carbon dioxide on the heart in an intact organism is opposed by sympathetic discharge stimulated by direct cerebral hypercapnia. Isolated cerebral hypercapnia produces increased myocardial contractility tachycardia and peripheral vasoconstriction (34). On the other hand, beta-adrenergic blockade was not found by Wendling *et al.* (131) t prevent the increase f cardiac output during hypercapnia. Carbon dioxide may depress myocardial function by inhibiting the citric acid cycle and by reducing the oxygen supply by y of the Bohr shift.

The data on cardiac output during hypercapnia are contradictory. According to most reports, the cardiac output increases in man (6, 42, 83, 102, 104) and dog (18). In contrast, Auld t al. (10) did not find any changes in cardiac output, heart rat or peripheral resistance in anesthetized children during hypercapnia. Sentarinen (121) observed both increased, decreased and unchanged cardiac outputs in h perc pnic dogs.

The hyperventilation that occurs at increased carbon dioxide levels may change he cardiac output response, bec use hyperventilation ma increase cardiac output even in h percapnia (8., 104).

Carbon dioxide usuall increases the heart rate in man (10?) but ma cause bradycardia i the dog 9., 121). This may be direct effect on the heart, because Downing *et al.* (34) *found that isolated* h percapnia f he central nervous system of dog results in tachy rdia.

Arterial pressure increases slightly during hyper capnia. This is due to an increased cardiac output in spite f peripheral vasodilatation. Hypotension that ften *occurs after experimental hypercapnia* 110 is most pronounced after the arterial pCO_2 has exceeded 50 mmHg.

Tolerance f high pCO_2 seems to be good in dogs provided hat oxygenation is sufficient. Nahas t al. (91) observed increase in cardiac output 63 per cent and marked bradycardia (28 per ce t decrease) fter 15 minutes of pnic oxygenation t p CO_2 of 120 mmHg. The survival tm in these conditions may be as long as 53 minutes in dogs with pCO_2 of nearly 400 mmHg nd blood pH f 6.5 6.6 (73).

onduction disturbances, extrasystoles, ingravity abnormal atrial and nodal activity (51) and even ventricular fibrillation (17) ha been observed in man during hypercapnia. The disturl nces ha been attributed t increased serum potassium concentration (78) but this explanation has not been generally accepted (99).

Hypercapnia during the fetal and neonatal periods

Intrauterine asphyxia consists partly f hypercapnia. The influence of isolated hypercapnia in human *fetuses* has not been investigated. Assali t al. (8) ventilated pregnant ew with carbon dioxide and found that the arterial pCO_2 increased, the arterial blood pressure rose and the carotid, femoral and umbilical blood flow increased in the fetuses. These changes possibly indicate an increased cardia output.

Increased cardiac *output* has been observed in neonatal lambs during hypercapnia also the heart rate and central blood olume are elevated (, 117). Hypercapnia does not, however *alter the stat f the* arterial duct (96).

EFFECTS OF METABOLIC ACIDOSIS ON THE BLOOD CIRCULATION

The cardiac output is low in dogs suffering from metabolic acidosis (18, 40) but Holmeth (104) and Richardson *et al.* (102) did not find changes in cardiac output in men fter infusion f small amounts f lactic or hydrochloric acid. Richardson t al. *observed an increased cardiac output in men after the* infusion f sodium bicarbonate.

A decreased cardiac output has been attributed t decreased myocardial contractility in dogs suffering from metabolic acidosis (27). The heart functio slows dow less in intact animals than in isolated heart (49 93). *However metabolic acidosis does not* significantly alter the entricular function in full-grow cats (36) and newborn lambs (37) after extend surgery.

The greater ability of an intact organism to withstand low pH is thought t be due to the function f the sympathetic nervous system. However Downing *et al.* (36) observed an increased *entricular function* hen the cerebral blood supply as interrupted. They concluded that lower sympathetic centers begin t function. This view is substantiated by the observation that lactic acid infusion usually produces tachycardia and increased arterial pressure corresponding t that produced by the injection *f 2 µg/kg f epinephrine* these responses are no longer obtained after the removal f the adrenals (137).

Acidosis ma *suppress* myocardial function by diminishing carbohydrate uptake (49, 9.) or may lower the oxygen supply to the myocardium by

electromagnetic flowmete fo newborn cal es with normal cid base balance (10.) and for neonatal lambs with normal acid base balance when the dye dilution method was used (11) In contrast the preliminary esults of Kol ikko (72) show that cardiac output increases during moderate hypoxia in neonatal lambs when cid base conditions are normal.

The central blood volume increases in neonatal lambs during hypoxia according to preliminary results of Kolvikko (2) More recently Stahlman *et al.* (117) measured pulmonary blood volumes by th slope method and reported decreased values luri g hypoxia.

There are data which indicate that th diving pattern may occur also in f tuses and ewborn in fants. Bradycardia which may be due to brain co pression n l reduced cerebral blood flow is observed in human fetuses during uterine contractions (87) Bradycardia continues lo ge than the uterine co traction period in asphyxiated fetuses. This bradycardia may be preve ted with at opine (87) Also the diving bradycardia f seals is preve ted by this drug (40) The lactic aci l concentration of the blood f human infants remains low during delivery but increases immediately aft rwards (63 71) This ariation of the lactic acid concentrati n during and fter delivery may reflect peripheral vasoconstriction imilar to that observed in di ing animals. According to Celander (20) breathing of gas mixtures co taining less than 15 pe cent o ygen produces a decreased blood flow in the limbs and tachycardia at the same time in infants but then, for a while pro ounced bra ly cardia. This kind of adjustment of the periph ral circulation requires a mature centrally co trolled asoconstriction. Already at this age the peripheral ascular bed co tra t on infusion of norepinephrine (09)

Hypoxia or asphyxia in fetal lambs at term leads to increased arterial pressure, bradycardia, and decreased femoral arterial and increased carotid and umbilical arterial blood flow (8) Elsne *et al* (40) observed a diving pattern in oonatal calves, but t bef re the 10th day of life.

Effects of acid base changes on the response to hypoxia

The cardiac outputs of ewborn cal es decrease in hypoxia when th animals ha m taboli acidosis. The output reverts to normal when the acid base abnormality and hypoxemia are corrected (10.) Similar results w re btained by K ivikko (72) fo newborn lambs. As found by Dow ing *et al.* in cats (36) and newborn lambs (37) the decrease seems to be due to decreased myocardial co tractility in these conditions. In the experiments of Downing *et al.*, hypoxia o cidemia alone did not depress the myocardial co tractility significantly but the combined ffect of these co ditions was a markedly depressed entricula function. This depression was less in ewborn lambs than in dult cats, which possibly indicates a bett ana robic capacity in the former

The reason for th decreased myocardial contractility is ot clea The factors maintaining the contractility are an adequate supply of oxygen nd glucose for the en rgy metabolism of the heart and proper functio of the sympathetic nervous system. In acidosis, in respiratory as w ll in metabolic, the Bohr shift may decrease the myocardial oxygen supply In severe asphyxia the myocardial glycogen tores may be depleted e tirely and the ability to utilize blood glucose may be reduced (47) The central nervous ystems has certain regulatory effect on the myocardial co tractility According t Downing *t al.* (36) occlusion of the cerebral blood flow during hypoxia associated with metabolic cidosis causes a further decrease in yocardial contractility

CARDIOVASCULAR ADJUSTMENTS DURING ACUTE HYPERCAPNIA

Hypercapnia in adults

Carbon dioxide removal is ot impaired by a moderate decrease in cardiac outp t (54) This may be ex plained by an effecti e transport of arbon dioxide to the lungs. In pite of the small potential danger of carbon dioxide ret ntion the carbon dioxide level seems to be a ery stro g regulator of both local nd e t l circulation. The quick changes in entilation and circulation seen in hypercapnia tend t normalize the acid base conditions. The main sites where carbon dioxide xerts its ffects are the art ioles, the heart, the adrenals, and the chemorecept rs f the orta, carotid sinus and brain.

Carbon dioxide gene lly induces dilatation f the arterioles. This effect is particularly strong in the cerebral circulati n, but seems to be weaker in the coronary circulatio (106)

Carbon dioxide has a depressant effect on an isolated heart (99) Bonif ce and Brow (15) observed that entilation f 5 t 50 per cent carbo dioxid by open-chest dogs resulted in 13 to 50 pe cent decrease in the tricular co tractile f rce The response to carbon dioxide has ften been observed to be the reverse aft less ext nal surgery As I monstrated I y N has and Ca rt (93) the reaso fo this seems t be an increased ympathetic actio

The Aims of the Study

The aims of the present study were to determine

— the basal values of the cardiac output heart rate, stroke volume central blood volume the ratio of stroke volume to central blood volume and the circulation time in sheep from birth to the age of one year

— the influence of chloralose anesthesia on the blood circulation of neonatal lambs and their cardiovascular responses to hypoxia and hypercapnia,

— the cardiovascular response of neonatal lambs and, for comparison sheep up to the age of one year to acute arterial hypoxia,

— the influence of metabolic acidosis on the cardiovascular response of neonatal lambs to hypoxia,

— the circulatory response of neonatal lambs and sheep to hypercapnia,

— the influence of metabolic acidosis on cardiovascular functions in newborn lambs.

limiti g the formation of oxyhemoglobin. A high acidity does not seem to depress the myocardial response to infused norepinephrine (35)

The effect of metabolic acidosis seems to have been investigated less in the fetal a d neonatal periods than later in life. Metabolic acidosis produced by lactic acid infusion decreases cardiac output in newborn cal es; correction of the acid base status with bicarbonate raises the cardiac o tput to normal again (103) Treatme t of infa ts suffering from respiratory distress with alkali and glucose (124) has been observed to decrease mortality (1.5) The same treatment improves the cardio ascular functions of newborn monkeys suffering fro e perimental asphyxia (2)

EFFECTS OF CHLORALOSE ANESTHESIA ON THE CIRCULATION

Chloralose is commonly considered one of the best anesthetics in circulation studies. Howe it has been observed to increase the heart rate by 40 p cent nd to correct respiratory and other also arrhythmias (80) v Ludany considered that there is a synergism between chloralose and epinephrine with ut however presenting a y direct evidence for his statement (80)

Shabetai *et al.* (11.) observed that chloralose may change the cardiac output by 25 to 40 per cent. In co trast Wiggers (133) reported no changes in cardiac output following the administration of chloralose.

Chloralose has been the agent most commonly used to produce general anesthesia in newborn lambs. Cross *et al* (20) observed that newborn lambs need considerably less of this ge t tha older sheep for sufficient nesthesia.

On the basis of xtensi e studies of hypoxia in rabbits, Korner (73) pointed out the importance of not using anesthesia during perimental hypoxia, because nesthesia greatly alters the ffect of hypoxia on the circulatio i these nimals.

The Aims of the Study

The aims of the present study were to determine

— the basal values of the cardiac output heart rate stroke volume central blood volume the ratio of stroke volume to central blood volume and the circulation time in sheep from birth to the age of one year

— the influence of chloralose anesthesia on the blood circulation of neonatal lambs and their cardiovascular responses to hypoxia and hypercapnia,

— the cardiovascular response of neonatal lambs and, for comparison, sheep up to the age of one year to acute arterial hypoxia,

— the influence of metabolic acidosis on the cardiovascular response of neonatal lambs to hypoxia,

— the circulatory response of neonatal lambs and sheep to hypercapnia,

— the influence of metabolic acidosis on cardiovascular functions in newborn lambs.

limiting the formation of oxyhemoglobin. A high acidity does not seem to depress the myocardial response to infused norepinephrine (35)

The effect of metabolic acidosis seems to ha e been investigated less in the fetal a d neonatal periods than later l life. Metabolic acidosis produced by lactic acid infusion decreases ardiac output in newborn calves correction of the acid base status with bicarbonate raises the cardiac output to normal again (103) Treatment of infants suffering from respiratory distress with alkali and glucose (1 4) has been observed to decrease mortality (1_3) The same treatment improves the cardio ascular fun tions of newborn monkeys suff ri g from experi ental asphyxia (8)

EFFECTS OF CHLORALOSE ANESTHESIA ON THE CIRCULATION

Chloralose is commonly considered one of the best anesthetics in circulation studies. Howeve it has been observed to increase the heart rate by 41 per cent and to correct respiratory and other minor arrhythmias (80) v Lukany considered that there is a synergism between chloralose and epinephrine without however presenting any direct evidence for his t tement (80)

Shabetai *et al.* (11) observed that hloralose may cha ge the cardiac output by 25 to 40 per cent. In contrast Wiggers (133) reported no changes in cardiac output following the administration of chloralose.

Chloralose has been the agent most commonly used to produce ge eral anesthesia in ewborn lambs. Cross t al (96) observed that ewborn lambs need considerably less of this gent than older sheep for sufficient anesthesia.

On the basis of e tensi studies f hypoxia in rabbits, Korner (73) pointed out the importan of not using anesthesia during perimental hypoxia, because anesthesia greatly alt rs th ffect of hypoxia o the circulation i these nimals.

The Aims of the Study

The aims of the present study were to determine

— the basal values of the cardiac output, heart rate, stroke volume, central blood volume, the ratio of stroke volume to central blood volume and the circulation time in sheep from birth to the age of one year

— the influence of chloralose anesthesia on the blood circulation of neonatal lambs and their cardiovascular responses to hypoxia and hypercapnia,

— the cardiovascular response of neonatal lambs and, for comparison, sheep up to the age of one year to acute arterial hypoxia,

— the influence of metabolic acidosis on the cardiovascular response of neonatal lambs to hypoxia,

— the circulatory response of neonatal lambs and sheep to hypercapnia,

— the influence of metabolic acidosis on cardiovascular functions in newborn lambs.

limiting the formation of oxyh moglol in. A high acl lity loes not seem to depress the myocardial response to infused norepinephrine (35)

The effect f metabolic acidosis seems to have been investigated less in the fetal nd neonatal periods than late in life. Metabolic acidosis produced by lactic aci l infusion decreases cardiac output in newborn cal es correction of the acid base st tus with bicarbonate raises the cardiac output to normal again (103) Treatment of infant suffering from respiratory distress with alkali and glucose (1 4) has been observed to decrease mortality (1–5) The same treat ent improves the cardiovascular functi n of newborn mo keys suffering from experimental asphyxia (^)

EFFECTS OF CHLORALOSE ANESTHESIA ON THE CIRCULATION

Chloralose is commonly considered one of the best anesthetics in irculation tudies. However it has been observed to increase the heart rate by 43 per cent an l to correct respiratory and other minor arrhythmias (80) v Ladany considered that there is a ynergism between chloralose and e inephrine witho t however presenting a y direct evidence for his statement (60)

Shabetai t *al.* (11) observed that chloralose may cha ge the cardiac output by –5 to 40 per ce t In co trast Wiggers (133) reported no changes in cardiac output following the admi istration of chloralose.

Chloralose has been the age t most comm nly used to produce general anesthesia in newborn lambs. Cross *et al.* (^0) observed th t newborn lambs need c nsiderably less of this ag nt than olde sheep for sufficient anesthesia.

On the basis f extensi studies of hypoxia in rabb its, Korner (73) pointed out the importance of not using anesthesia luring xperimental hypoxia because anesthesia greatly alt rs the effect of hypoxia a the circulatio in these animals.

TABLE III The animals us l in the present stu ly an l the experiments done on them

	Number of animals	Age mean and range	Anesthetized	Unanesthetized	Respirator used
Whole series	67				
Rejected cases	13				
Qualified cases	34				
Lambs	43	5.0 day (1.3—43)	25	17	7
Hypoxia	—	6.0 days (1.5—20	16	9	3
— group A	10	7.2 days 1.3—20)	3	3	3
— group B	11	6.0 day —14	8	3	1
— group C	4	3.1 days (1.5—7)	3	1	4
Hypercapnia	14	6.0 day (1.3— 4	8	6	
Metabolic acidosis	9	4.9 day 1.3—9	9	1	
Sheep	9	9.0 months (6—1	1	8	
Hypoxia	6		1	6	
Hypercapnia	2			2	

Four sedated ith hemlutol[8]
Sedated with hemlutal[3]

Material

Sixty-seven lambs and sheep were employed in the present study. Of these, 13 animals were rejected later on various grounds which included death during an experiment, technical errors in dye dilution recordings, poor condition of the animal and abnormal cardiovascular patterns. Qualified results were thus obtained from 54 animals (Table III).

At the beginning of each experiment the basal circulatory values were determined. At this moment the animals had to be in good condition with a normal acid-base status (pCO_2 40 ± 5 mmHg and B.E. ± 3 meq./l.) and without any signs of fetal shunts in the dye curves. Also cardiac arrhythmias (as, for example, in the case presented in Fig. 18) led to exclusion from the series.

LAMBS

The number of lambs was 45, of which 23 were females and 22 males. The age distribution is presented in Table III. Lambs less than 36 hours old were not used in order to avoid fetal shunts. All of the lambs had been delivered vaginally and were apparently in good condition. The following experiments were carried out on the lambs.

Hypoxia experiments were conducted with 25 animals. The animals were divided into three groups according to the degree of metabolic acidosis that developed. Group A comprised those with a base excess (B.E.) from 0 to —5 meq./l., group B those with a B.E. from —5 to —10 meq./l. and group C those with a B.E. less than —10 meq./l. The age distribution is shown in Table III.

Hypercapnia was induced in 14 animals qualified for the analysis of the response. The cases presented in Figs. 17 and 18 were excluded because of cardiac arrhythmias.

Metabolic acidosis developed in 9 lambs so that it was possible to follow its progress by determining acid-base values.

A respirator was used in some hypoxia experiments to counteract the effect of hyperventilation on pCO_2. It was used also in 4 hypercapnia experiments to produce higher carbon dioxide levels in the arterial blood and prevent hyperventilation. If a lamb was in such a condition that it required a respirator, it was excluded from the series.

SHEEP

The term sheep as used here refers to animals from 6 to 12 months old. Of the 9 sheep studied, 4 were females and 5 males. Anesthesia was induced with chloralose in one case, mild sedation with Sombutol® in 4 cases, and no sedation in 4 cases. Hypoxia and hypercapnia experiments were carried out on the sheep. Metabolic acidosis did not develop in any of the sheep.

TABLE III The animals used in the present study and the experiments done on them

	Number of animals	Age mean and range	Anesthetized	Unanesthetized	Respirator used
Whole series	67				
Rejected cases	13				
Qualified cases	54				
Lambs	45	3.0 day (1.5—43)	[illegible]	17	
Hypoxia	25	6.0 day (1.5—20)	16	9	7
— group A	10	7.2 days (1.5—20)	3	5	3
— group B	11	6.8 days (?—14)	8	3	3
— group C	4	3.1 day (1.5—7)	3	1	1
Hypercapnia	14	6.0 day (1.5—4)	8	6	4
Metabolic acidosis	9	4.9 day (1.5—9)	8	1	
Sheep	9	8.0 months (6—1)	1	8	
Hypoxia	6		1	6	
Hypercapnia	3			2	

Four sedated with Nembutal ®
Sedated with Nembutal ®

Material

Sixty-seven lambs and sheep were employed in the present study. Of these, 13 animals were rejected later on various grounds which included death during an experiment, technical errors in dye dilution recordings, poor condition of the animal and abnormal cardiovascular patterns. Qualified results were thus obtained from 54 animals (Table III).

At the beginning of each experiment the basal circulatory values were determined. At this moment the animals had to be in good condition with a normal acid-base status (pCO_2 40 ± 5 mmHg and B.E. ± 3 meq./l.) and without any signs of fetal shunts in the dye curves. Also cardiac arrhythmias (as, for example, in the case presented in Fig. 18) led to exclusion from the series.

LAMBS

The number of lambs was 45, of which 23 were females and 22 males. The age distribution is presented in Table III. Lambs less than 36 hours old were not used in order to avoid fetal shunts. All of the lambs had been delivered vaginally and were apparently in good condition. The following experiments were carried out on the lambs.

Hypoxia experiments were conducted with 25 animals. The animals were divided into three groups according to the degree of metabolic acidosis that developed. Group A comprised those with a base excess (B.E.) from 0 to —5 meq./l., group B those with a B.E. from —5 to —10 meq./l. and group C those with a B.E. less than —10 meq./l. The age distribution is shown in Table III.

Hypercapnia was induced in 14 animals qualified for the analysis of the response. The cases presented in Figs. 17 and 18 were excluded because of cardiac arrhythmias.

Metabolic acidosis developed in 9 lambs so that it was possible to follow its progress by determining acid-base values.

A respirator was used in some hypoxia experiments to counteract the effect of hyperventilation on pCO_2. It was used also in 4 hypercapnia experiments to produce higher carbon dioxide levels in the arterial blood and prevent hyperventilation. If a lamb was in such a condition that it required a respirator it was excluded from the series.

SHEEP

The term sheep as used here refers to animals from 6 to 12 months old. Of the 9 sheep studied, 4 were females and 5 males. Anesthesia was induced with chloralose in one case, mild sedation with Sombutol® in 4 cases, and no sedation in 4 cases. Hypoxia and hypercapnia experiments were carried out on the sheep. Metabolic acidosis did not develop in any of the sheep.

Hypercapnia was induced by ventilation with air containing 10 per cent carbon dioxide through the face mask or respirator.

Dye dilution curves were recorded at intervals of 1 to 5 minutes during the experiments.

The removed blood samples were as small as possible. The total blood removed from a lamb varied from 5 to 1 ml and was replaced with saline or with blood from the ewe. The blood removed from the sheep was considered so small in volume that it was not replaced.

DYE DILUTION EQUIPMENT AND PROCEDURES

For the recording of the dye dilution curves, a densitometer-preamplifier system was designed and built. A reflecting instrument for the measurement of absorption at a wavelength of 805 nm (manufactured by Kipp & Zonen) was modified into a transmittance densitometer. A special preamplifier was built to obtain a linear relationship between dye concentration and pen deflection. This preamplifier was a long-tailed pair amplific. The input impedance of the preamplifier was adjusted so that a nearl linear response was obtained for dye concentration up t 10 mg per lite. By matching the transistors carefully it was possible to reduce the drift to less than ±0.5 per cent of the full-scale deflection per minute when the densitometer tracing was being recorded. To remove high frequency disturbances from the dye curve a filter was connected at the input of the preamplifie. This made the system slightly sluggish: the 95 per cent response time for sudden changes in densitometer output was 0.22 to 0.4 seconds. To minimize the sluggishness of the response the figure of merit f the sampling catheter was held at less than 0.4 seconds. The total volume of the cathete and cuvette was 0.5 ml. The blood was drawn through them at a constant rate f 39 ml per minute. The catheter transit time was 0.6 seconds. The 90 per cent response time for a square d e wave was 1.0 seconds. The system was very sensitive to flow rate: the change in deflection caused by a change in flow from 0 t 39 ml per minute was at most 10 per cent f the full-scale deflection.

The bl od was withdrawn through the densitometer cuvette with an Atlas constant speed withdrawal-infusion pump which drew water from the lower end of a chamber which caused blood to flow onto a rubber diaphragm within the chamber. The amount of blood withdrawn from the lambs was about 15 ml and that withdrawn from the sheep up to 30 ml. The blood was returned to the artery and the blood loss was practically nil.

The dye dilution apparatus was calibrated with 10 ml of arterial blood containing 0.0_5 mg of Cardio-Green[*]. This blood was drawn through the cuvett from a syringe at a rat f 39 ml per minute. The base line was obtained by passing arterial blood through the cuvette from another syringe. The calibration was done in duplicate on two occasions during the series f experiments with each animal. The separate calibration readings usually agreed very well with ea h other.

Solutions of Cardio-Green[*] containing 1.25 r _5 mg f the dye per ml were injected. Amounts of 0.06 to 0.08 mg f dye per kg of body weight were sufficient to produce good curves. The injected volume did not exceed 1 ml.

The recording of the dye dilution curves was done with a Sanborn recorder (model 150) connected to an AC DC preamplifier (model 150—1000). The maximal deflection obtained with this recorder was only 50 mm which was found somewhat troublesome because overshooting occurred or curves of low amplitude resulted.

Cardio Green[*] (Hynson, Westcott & Dunning, Inc., Baltimore Maryland)

Methods

PREPARATION

The *preparation* of the animals was usually begun with the insertion of catheters under local Anestecain®* anesthesia one catheter was inserted into a femoral artery and further to a point close to the aortic bifurcation for withdrawing blood through a densitometer and two catheters were inserted into the superficial jugular vein until they entered the *right atrium* one for injection of dye solution and the other for infusion of other solutions. The actual locations of the catheter tips were controlled at autopsy To prevent coagulation of blood in the catheters, 1 ml of heparin was injected into the latter at intervals of 1 to 2 hours.

When general anesthesia was induced, chloralose 20 to 50 mg/kg was injected into a major vein of the lamb The anesthesia was maintained as light as possible but shivering was suppressed General anesthesia was given to all lambs which were to be subjected to tracheotomy and artificial respiration in order to avoid vagal blocks. Lambs not subjected to general anesthesia usually remained calm sucking the finger of one of the team members was often sufficient to calm an animal However the animals were sometimes restless during periods of hypoxia *and hypercapnia*

Administration of Sombutol®* (2 to 4 mg/kg of barbiturate) was used to produce a mild sedation in some of the sheep Formation of gas in the stomach and intestines was so strong in some of the sheep that puncture with a large needle was necessary to prevent difficulty in breathing

To prevent a spontaneous fall in body temperature *the lambs* were placed on a warm plate The temperatures of animals were controlled with electronic equipment using rectal electrodes (manufactured by Elektrolaboratoriet, Copenhagen) The temperatures of the animals varied between 39 and 41 C but variations exceeding 1 C did not occur in any animal Slight decreases in temperature occurred in the hypoxia experiments.

Needle electrodes were used when recording ECG's with a Sanborn four-channel recorder (model 150) connected to an ECG *preamplifier* The paper speed of 25 or 5 mm per second used to record the dye curves was sufficient to permit calculation *of the heart* rate and to detect gross abnormalities in cardiac rhythm

EXPERIMENTS

Hypoxia was induced by ventilating the lambs with 10 per cent oxygen in nitrogen through a mask applied to the nose When a respirator (manufactured by C F Palmer London) was used, the gas mixture was administered through it In the experiments with the sheep tracheotomy was not done nor was the *respirator used the gas mixture was supplied through a mask*

Anestecain® (Lidocaine) manufactured by Lääke Oy Turku Finland

Sombutol® (mebumal 0.030 mebumal ent 0.0672, urethan 0.250 pirfort. 0.130 glycerol 0.125 phenylcarbinol 0.013 per ml) manufactured by Lääke Oy Turku, Finland.

Hypercapnia was induced by ventilation with air containing 10 per cent carbon dioxide through the face mask or respirator.

Dye dilution curves were recorded at intervals of 1 to 5 minutes during the experiments.

The removed blood samples were as small as possible. The total blood removed from a lamb varied from 5 to 15 ml and was replaced with saline or with blood from the ewe. The blood removed from the sheep was considered so small in volume that it was not replaced.

DYE DILUTION EQUIPMENT AND PROCEDURES

For the recording of the dye dilution curves, a densitometer preamplifier system was designed and built. A reflecting instrument for the measurement of absorption at a wavelength of 805 nm (manufactured by Kipp & Zonen) was modified into a transmittance densitometer. A special preamplifier was built to obtain a linear relationship between dye concentration and pen deflection. This preamplifier was a long-tailed-pair amplifier. The input impedance of the preamplifier was adjusted so that a nearly linear response was obtained for dye concentration up to 10 mg per liter. By matching the transistors carefully it was possible to reduce the drift to less than ±0.5 per cent of the full-scale deflection per minute when the densitometer tracing was being recorded. To remove high frequency disturbances from the dye curve a filter was connected at the input of the preamplifier. This made the system slightly sluggish: the 93 per cent response time for sudden changes in densitometer output was 0.22 to 0.4 seconds. To minimize the sluggishness of the response the figure of merit of the sampling catheter was held at less than 0.4 seconds. The total volume of the catheter and cuvette was 0.5 ml. The blood was drawn through them at a constant rate of 39 ml per minute. The catheter transit time was 0.6 seconds. The 90 per cent response time for a square dye wave was 1.0 seconds. The system was very sensitive to flow rate: the change in deflection caused by a change in flow from 0 to 39 ml per minute was at most 20 per cent of the full-scale deflection.

The blood was withdrawn through the densitometer cuvette with an Atlas constant speed withdrawal-infusion pump which drew water from the lower end of a chamber which caused blood to flow onto a rubber diaphragm within the chamber. The amount of blood withdrawn from the lambs was about 15 ml and that withdrawn from the sheep up to 30 ml. The blood was returned to the artery and the blood loss was practically nil.

The dye dilution apparatus was calibrated with 10 ml of arterial blood containing 0.065 mg of Cardio-Green[a]. This blood was drawn through the cuvette from a syringe at a rate of 39 ml per minute. The base line was obtained by passing arterial blood through the cuvette from another syringe. The calibration was done in duplicate on two occasions during the series of experiments with each animal. The separate calibration readings usually agreed very well with each other.

Solutions of Cardio-Green[a] containing 1.5 or 2.5 mg of the dye per ml were injected. Amounts of 0.06 to 0.09 mg of dye per kg of body weight were sufficient to produce good curves. The injected volume did not exceed 1 ml.

The recording of the dye dilution curves was done with a Sanborn recorder (model 150) connected to an AC-DC preamplifier (model 150—1000). The maximal deflection obtained with this recorder was only 50 mm, which was found somewhat troublesome because overshooting occurred or curves of low amplitude resulted.

---

[a] Cardio-Green® (Hynson, Westcott & Dunning, Inc. Baltimore, Maryland)

OTHER MEASUREMENTS

The variation of the arterial oxygen saturation during the hypoxia experiments was followed by measuring it in duplicate samples with a Brinkman hemoreflector (Kipp & Zonen)

Acid base changes were followed by taking samples from the femoral artery at frequent intervals during the experiments, especially during the hypercapnia periods. These were sealed in airtight syringes. The actual pH actual pCO_2 standard bicarbonate level and base excess were measured as proposed by Siggaard Andersen et al (113) and Siggaard Andersen and Engel (114) within 1 to 2 hours of sampling

CALCULATIONS

The recorded dye dilution curves were accepted for calculations when there were no signs of marked shunts in any direction and when signs of recirculation were noted after the descending limb of the curve had fallen below 50 per cent of the maximum amplitude of the curve (60)

Signs of small right to-left or left to-right shunt flows were noted in the youngest lambs. These were ignored when it was apparent that the errors could not exceed 5 per cent

The cardiac outputs (CO) were calculated from the Stewart Hamilton equation

$$CO = \frac{60 \cdot I}{\bar{c} \cdot t}$$

in which I is the amount of dye injected (mg) c the mean concentration of dye (mg per liter) during the primary curve and t the duration of the primary curve in seconds. $\bar{c} \cdot t$ was obtained by measuring the area under the primary curve with a planimeter and dividing the area by a calibration factor

The primary curve was separated from the recirculation wave in the normal way by extrapolating the declining slope on semilogarithmic paper

The heart rate was calculated from ECG tracings which were recorded at the same time as the dye dilution curves on the same paper

The *stroke volume* was obtained by dividing the *cardiac output* by the heart rate

The appearance time was obtained by *subtracting* the catheter transit time (0.6 seconds) from the recorded appearance time

The mean transit time (MTT) was calculated according to Hamilton (56) and Meier (86)

$$MTT = \frac{\Sigma c \cdot t}{\Sigma c}$$

The central blood volume (CBV) was calculated from

$$CBV = CO \cdot MTT$$

The relationship between the appearance time and the ratio of central blood volume to the cardiac output can be easily investigated by comparing AT and MTT. The assumed relationship may be expressed by

$$AT = \frac{k \cdot CBV}{CO}$$

On substituting CBV = CO MTT in this equation it follows that

$$AT = k \cdot MTT$$

Thus a linear relationship must exist between AT and MTT if the initial assumption is valid

The statistical treatment of the data was done by applying Student's t test. Regression lines were fitted to the data with an IBM 1130 computer. A difference was considered almost significant when $p < 0.05$, *significant* when $p < 0.01$ and highly significant when $p < 0.001$

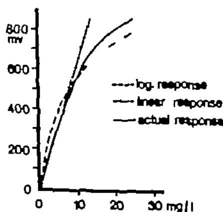
TESTS OF THE DYE DILUTION EQUIPMENT

The linearity of the *densitometer-preamplifier* response was tested with known amounts of Cardio-Green[®] in blood. The results are presented in Fig 1 The linearity was satisfactory up to a dye concentration of 10 mg per liter The logarithmic and linear responses are also presented in Fig. 1 It will be seen that the response curve of the apparatus deviates from linearity 8 per cent at a dye concentration of 10 mg per liter In practice the height of the curve usually corresponded to from 4 to 8 mg of dye per lit r and never exceeded 10 mg per liter

The dye dilution apparatus was tested with an artificial flow system using volumes of 60 to 140 ml. *The flow through this system coul l* be calculated with an error f less than ± 1 per cent as illustrated in Fig. .. The accuracy of the flow measurements was independent of the volume of the artificial system. The *flow* rate in a tube 1400 ml in volume could be measured with the same accuracy

Volume measurements in the range from 60 to 140 ml in the artificial flow system did not give satisfact ry results, because of uneven distribution of the dye However the volume f a plastic tube of 1400 ml capacity could be measured with satisfactory accuracy The errors were less than ± 1 per cent. The dye lilution apparatus was thus considered sufficiently accurate for measurements of b th flow rate and volume

Duplicate determinations of cardiac output with lambs in a st ady stat showed that the maximum error was ± 1 per cent and S.D ; 6 per cent



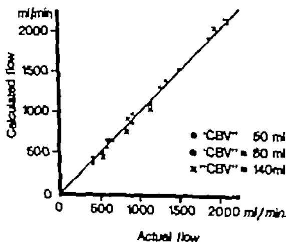


Fig 1 (left) The response f the densitometer to hanges in the dy concentration f hole blood (solid line The logarithmic (broken line) and linear (dash-dot line) responses are also dra n.

Fig 2 (right) The reproducibility f flow measurements with the d dilution equipment in an artificial flow system using ater as medium. The results obtained using different olumes are indicated by differ nt symbols.

OTHER MEASUREMENTS

The variation of the arterial oxygen saturation during the hypoxia experiments was followed by measuring it in duplicate samples with a Brinkman hemoreflector (Kipp & Zonen).

Acid-base changes were followed by taking samples from the femoral artery at frequent intervals during the experiments, especially during the hypercapnia periods. These were sealed in airtight syringes. The actual pH, actual pCO_2, standard bicarbonate level and base excess were measured as proposed by Siggaard Andersen *et al.* (113) and Siggaard Andersen and Engel (114) within 1 to 2 hours of sampling.

CALCULATIONS

The recorded dye dilution curves were accepted for calculations when there were no signs of marked shunts in any direction and when signs of recirculation were noted after the descending limb of the curve had fallen below 30 per cent of the maximum amplitude of the curve (60).

Signs of small right-to-left or left-to-right shunt flows were noted in the youngest lambs. These were ignored when it was apparent that the errors could not exceed 5 per cent.

The cardiac outputs (CO) were calculated from the Stewart Hamilton equation

$$CO = \frac{60 \cdot I}{\bar{c} \cdot t}$$

in which I is the amount of dye injected (mg), $\bar{c}$ the mean concentration of dye (mg per liter) during the primary curve and t the duration of the primary curve in seconds. $\bar{c} \cdot t$ was obtained by measuring the area under the primary curve with a planimeter and dividing the area by a calibration factor.

The primary curve was separated from the recirculation wave in the normal way by extrapolating the declining slope on semilogarithmic paper.

The heart rate was calculated from ECG tracings which were recorded at the same time as the dye dilution curves on the same paper.

The stroke volume was obtained by dividing the cardiac output by the heart rate.

The appearance time was obtained by subtracting the catheter transit time (0.6 seconds) from the recorded appearance time.

The mean transit time (MTT) was calculated according to Hamilton (56) and Meier (86).

$$MTT = \frac{\Sigma c \cdot t}{\Sigma c}$$

The central blood volume (CBV) was calculated from

$$CBV = CO \cdot MTT$$

The relationship between the appearance time and the ratio of central blood volume to the cardiac output can be easily investigated by comparing AT and MTT. The assumed relationship may by expressed by

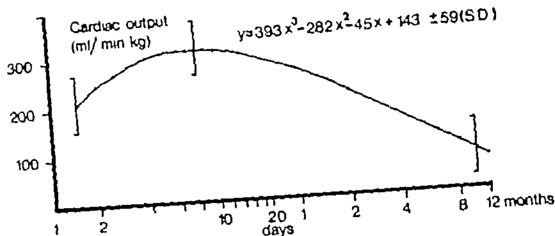
$$AT = \frac{k \cdot CBV}{CO}$$

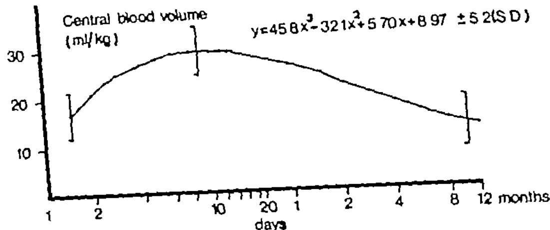
On substituting $CBV = CO \cdot MTT$ in this equation it follows that

$$AT = k \cdot MTT$$

Thus a linear relationship must exist between AT and MTT if the initial assumption is valid.

The statistical treatment of the data was done by applying Student's t test. Regression lines were fitted to the data with an IBM 1130 computer. A difference was considered almost significant when $p < 0.05$, significant when $p < 0.01$ and highly significant when $p < 0.001$.





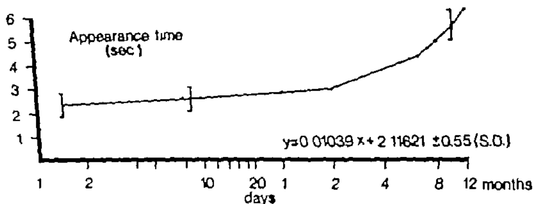


Fig. 3. Changes in cardiac output, central blood volume and appearance time with age in 43 lambs and 9 sheep. The lengths of the vertical bars are equal to 2 × S.D.

Results

BASAL CIRCULATORY VALUES IN NEONATAL LAMBS AND SHEEP

The circulatory parameters measured in lambs ($n = 45$) and sheep ($n = 9$) soon after their preparation were cardiac output heart rate stroke volume, central blood volume the ratio of SV to CBV and the dye appearance time The conditions that were to be fulfilled when the normal values of these quantities were measured are presented on p 18.

The mean cardiac output (Fig 3) in lambs one to two days old was about 200 ml/min kg It increased to 300 ml/min kg at the age of 8 days ($p < 0.05$) and then decreased steadily to 60 ml/min kg at the age of 12 months ($p < 0.001$)

The mean central blood volume (Fig 3) varied similarly with age as the cardiac output It increased from 16 to 28 ml/kg ($p < 0.001$) from the first to the ninth day and was 12 ml/kg in sheep 12 months old ($p < 0.001$)

The dye appearance time (Fig 3) increased linearly with age ($p < 0.001$) Its dependence on the central blood volume and the cardiac output was studied by the mathematical methods presented in the section on methods. The relationship between appearance time (AT) and mean transit time (MTT) was determined for all the animals ($n = 54$) up to the age of 12 months. As a linear correlation was found AT is directly proportional to MTT and hence to the ratio of central blood volume to cardiac output (Fig 4)

The heart rate stroke volume and the ratio SV/CBV were higher in unanesthetized lambs less than 30 days old than in sheep 6 to 12 months old (Table IV)

Effects of chloralose anesthesia on the basal values

Some of the values for unanesthetized and anesthetized lambs less than 30 days old can be compared in Table IV Chloralose did not significantly change the cardiac output (increase 3 per cent) central blood volume (increase 6 per cent) or the dye appearance time in lambs less than 30 days old. Significant differences in heart rate stroke volume and the ratio SV/CBV were observed between the animals that were and those that were not given chloralose (Table IV) The highest recorded heart rates in anesthetized lambs were 350 and 360 per minute in two lambs.

Similar results were obtained in the animals in which the parameters were measured before and immediately after administration of chloralose (Table V)

ARTERIAL HYPOXIA IN NEONATAL LAMBS

Changes in cardiovascular function

The experimental animals used in the hypoxia studies are presented in Table III The experiments ($n = 25$) were performed under moderate hypoxia with a mean S_aO_2 of 67 ± 5.1 (S D) per cent The changes in acid base values caused by hypoxia are presented in Tables VII and VIII Fig 5 presents the relationship between the arterial oxygen saturation and the cardiac output in cases where both were determined simultaneously The cardiac output increased clearly in most cases but decreases occurred as well In some animals the output doubled. The decrease ~

TABLE V Effects of chloralose on cardiac output heart rat stroke volume central blood volume ratio SV/CBV and appearance time in cases for which data were obtained before and after administration of the drug. The number of determinations is given in parentheses in the first column.

	Before anaesthesia	10 to 15 min after chloralose administration
Cardiac output, per cent (4)	100	97 (93—10_)
Heart rate beats per min (11)	1 ±40	22_±47
Stroke volume, per cent (4)	100	7_ (6_—_6)
CBV per cent (4)	100	93 (80—100)
SV/CBV per cent (4)	100	7 (6_—_6)
AT seconds (5)	2.0 (1.5—3.0)	_1 (1.7—_5)

When the B.E. was in the range from —5 to —10 meq. l. (Group B, n = 11) the cardiac output increased from 40 to 2_0 ml min kg and then decreased below the initial level. Neither change was statistically significant.

When the B.E. was less than —10 meq. l. (Group C n = 4) the output, 120 ml min kg was initially lower than in the other groups ($p < 0.001$) but did not change significantly during hypoxia.

To eliminate scatter of the values caused by age and metabolic acidosis, the hypoxia data were recalculated to obtain relative changes (Fig 7). In the calculations of the cardiac outputs, the initial relative standard deviation was taken to be 10 per cent. An initial relative S.D of 5 per cent was assumed for the heart rat and 10 per cent for stroke volume central blood volume and ratio SV/CBV. This treatment of the hypoxia data gave following results.

The cardiac output increased in group A by 31 to 3_ per cent ($p < 0.001$). The greatest increases were almost 100 per cent, but in one case the increase was only 10 per cent. No decreases from the initial level were observed. The cardiovascular pattern of one lamb of this group is presented in Fig 10.

In group B (B.E. —5 to —10 meq. l.) the cardiac output increased significantly less than in the former group ($p < 0.001$). The mean increase of about 10 per cent in this group did not prove significant. In some

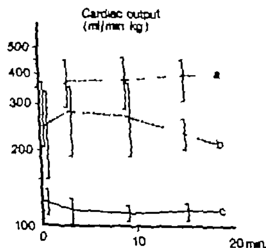


Fig 6 Changes in cardiac output during hypoxia ml min kg. Vertical lines are equal to 2 × S.D in each group.

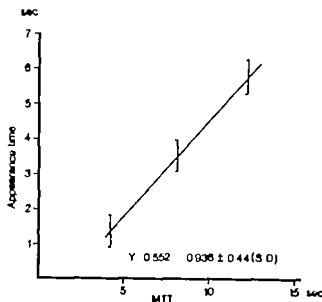


Fig 4 Correlati n between the ppearance time (AT) and the mean transit time (MTT) in lambs and sheep (n = 34) The lengths of the vertical lines are twice th tandard leviation.

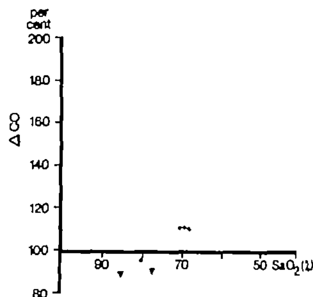


Fig Relationship between change in cardiac output and arterial oxygen saturatio (SO_2)
× group A (B.E. from 0 to —5 meq./l.)
group B (B.E. from —5 to —10 meq./l.)
▼ group C (B.E. less than —10 meq./l.)

curred only in animals with metabolic acidosis (B.E less than —5 meq /l)

The overall variation of the cardiac output in the hypoxia experiments was considerable (Fig 6) The initial output was determined by age (Fig 3) and the degree of metabolic acidosis (Fig 20) Furthermore increased acidity was observed to depress the response of cardiac output to hypoxia For this reason, the hypoxia material was divided into three groups according to base excess (B E.)

When the B E was more than —5 meq /l (Group A, n = 10) the mean cardiac output increased from 265 to nearly 400 ml/min kg ($p < 0.01$) and this level was maintained throughout the hypoxia period

TABLE IV Basal values (± S.D) of heart rate stroke volume and SV/CBV and the effect of chloralose on them The numbers of animals are given in parentheses

	Lambs 1.5 t 30 days kl	Sheep 6 t 1 mo ths old
Heart rat (pe minute)		
N anesthesia	185 ± .. (20)	140 ± 22 (9)
Chloralose	40 ± 43 (24)	
Difference du to anesthesia	.0 per cent ($p < 0.001$)	
Stroke vol m (ml/kg)		
No nesthesia	1 45 ± 0.32 (20)	0 60 ± 0.34 (9)
Chloralose	1 15 ± 0.32 (4)	
Difference due to nesthesia	1 per cent ($p < 0.001$)	
SV/CBV		
N nesthesia	0.060 ± 0 010 (20)	0.041 ± 0 008 (9)
Chloralose	0.045 ± 0.010 (4)	
Difference due t nesthesia	.3 per cent ($p < 0.001$)	

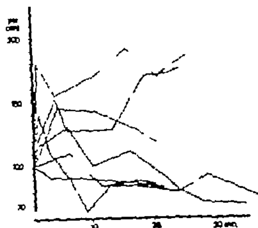


Fig. 8. Changes in cardiac output during hypoxia in lambs ventilated with respirator. Curves drawn with broken lines refer to group A (n = 3), dot-dash lines to group B (n = 2) and the solid line to group C (n = 1).

animals of this group the cardiac output increased up to 1.6 times the initial value but then invariably decreased close to the starting value or below it. This kind of cardiovascular pattern is presented in Fig. 12. In one case of this group the cardiovascular pattern was one which may be considered a diving pattern (Fig. 11). In this lamb insufficient breathing was associated with bradycardia and lowered cardiac output at the beginning of the hypoxia period.

In group C with severe metabolic acidosis (B.E. less than −10 meq./l.) the cardiac output decreased progressively during hypoxia ($p < 0.05$). In one of the four animals, the cardiac output increased at first by 5 per cent but decreased immediately afterwards. The mean change in cardiac output in the group differed significantly from that in group A ($p < 0.001$) and group B ($p < 0.05$).

The cardiac output curves of the lambs ventilated with a respirator during hypoxia are presented in *Fig. 8*. The cardiac outputs of these lambs that were prevented from becoming hypocapnic during the hypoxia period varied generally similarly as those of lambs that hyperventilated freely and became hypocapnic. The cardiac output *increased clearly* in the lambs of group A and the high level was maintained 20 minutes or more. In the lambs of group B the outputs increased at first, but then decreased clearly. In the only experiment with a lamb of group C in which the respirator was used, a decrease in cardiac output occurred.

The effect of *hypoxia on the heart rate* was a slight increase in all groups in spite of the large *differences in B.E. (Fig. 7)*. The mean increases were 6 to 13 per cent in different groups, but these were not significant. The variations of the heart rate were generally large (Table VI).

As seen in the uppermost section of Table VI a high degree of metabolic acidosis did not influence the initial heart rates. The variation of the heart rate was less in severe metabolic acidosis than in normal acid-base conditions. Thus, *increases of 4 to 13 per cent occurred in* group C (B.E. less than −10 meq./l.). In groups A and B (B.E. more than −10 meq./l.) increases of *20 to 40 per cent* occurred, but also considerable decreases occurred.

When the heart rate was initially high, the changes during hypoxia were small. All lambs with an initial heart rate exceeding 200 per minute were anesthetized with chloralose. When the initial heart rate varied from 150 to 230 per minute very large variations (both increases and decreases) in heart rate occurred during hypoxia in groups A and B.

The stroke volume (*Fig. 7*) increased by 18 to 25 per cent ($p < 0.01$) during hypoxia in group A and by about 5 per cent ($p < 0.05$) in group B. The change in the former group differed almost significantly from that in the latter group ($p < 0.05$). *In group C* a progressive decrease up to 19 per cent occurred ($p < 0.01$). This change differed from the change in *group B* ($p < 0.05$) and group A ($p < 0.001$).

The largest changes in stroke volume occurred in group *A* (+84 to −40 per cent)

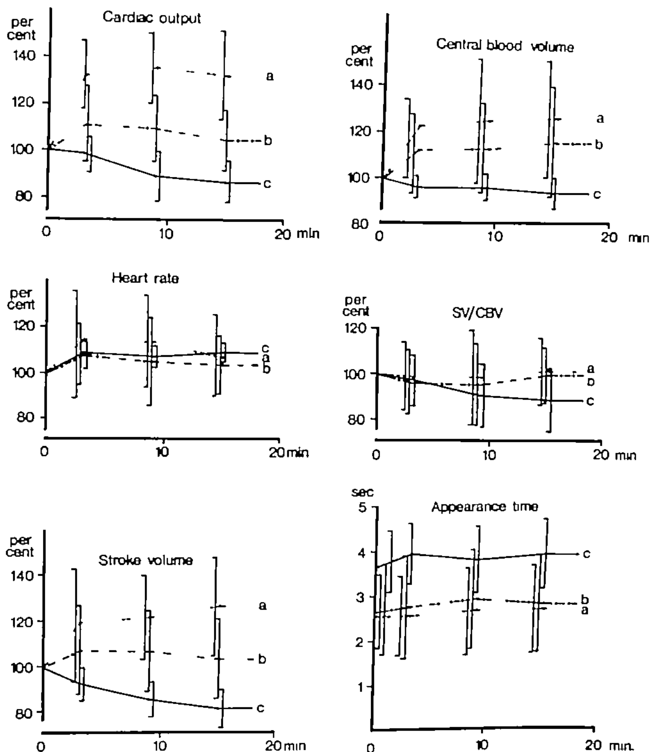


Fig 7 V riatio of cardia output heart rat stroke olume central blood ol me ratio SV CBV (per ce t) a l appearance time (seco ds) duri g hypoxia in neonat l lambs as a functio of time Group A ( ) (= 10) comprised animals with B F eding— meq/l group B (— — —) (= 11) those with B E. fro —3 t —10 meq /l an l gro p ((———) (= 4) those w th B.E. less tha —10 meq /l. The ertical lines are equal to 2 × S.D in ea h gro p

The ratio SV/CBV (Fig. 7) was calculated to find out whether changes in central blood volume affect the regulation of stroke volume. The mean decrease of this ratio during hypoxia was insignificant in all groups. Individual variations as large as ±40 per cent from the initial level occurred during hypoxia. The possible significance of the ratio will be discussed later.

The dye appearance time (Fig. 7) varied greatly in the lambs during hypoxia. No significant mean changes in this parameter from the initial values occurred in groups A, B, or C. The appearance times were longer in group C than in groups A and B owing to decreased cardiac output in severe metabolic acidosis (B.E. less than —10 meq./L). The mean appearance time in group C differed almost significantly from that in group A ($p < 0.05$).

Signs of fetal shunts were seen in the dye curves of four young lambs during hypoxia, but not constantly. A right-to-left shunt became evident when severe metabolic acidosis developed in one lamb that was excluded from the series.

Changes in acid-base balance

As mentioned before, the arterial oxygen saturation varied from 44 to 86 per cent (67 ± 5.1 per cent). The lambs which were supplied with 10 per cent oxygen through a

TABLE VII. Mean changes in acid-base balance during hypoxia in 17 lambs that hyperventilated freely. The ranges are given in parentheses in columns 2 and 3

	Before hypoxia	During hypoxia	Change
pH	7.33 (7.25—7.32)	7.30 (7.20—7.40)	
pCO_2 (mmHg)	37.2 (37—50)	31.8 (50—20)	—14 per cent ($p < 0.001$)
St. bicarbonate (meq./L)	20.0 (26.3—12.0)	19.1 (14.0—12.5)	—1 per cent ($p < 0.001$)
B.E. (meq./L)	—4.4 (+2 — —13)	—6.3 (0 — —16)	

TABLE VIII. Mean changes in acid-base balance during hypoxia in 5 lambs ventilated with a respirator

	Before hypoxia	During hypoxia	Change
pH	7.34 (7.29—7.43)	7.35 (7.27—7.40)	
pCO_2 (mmHg)	34 (33—35)	33 (29—39)	—0 per cent ($p > 0.05$)
St. bicarbonate (meq./L)	21 (23—19)	19.6 (20—17.3)	—11 per cent ($p < 0.01$)

TABLE VI Heart rate (beats per minute) response to hypoxia with reference to pre-experimental heart rate and degree of metabolic acidosis (groups A, B and C) The changes ar differences from the initial levels.

		Number of animals	Mean initial heart rate (range)	Mean change in heart rate at 3 min. (changes during 3 min.)	Mean change in heart rate at 10 min. (changes during 3—10 min.)	Mean change in heart rate at 15 min. (changes duri 10—15 min.)
The whole series	A	11	15 (170—310)	+30 (—40—+100)	+20 (—30—+130)	+10 (—50—+60)
	B	10	22[illegible] (1 0—300)	+[illegible]0 (—90—+80)	+5 (—90—+80)	+10 (—60—+60)
	C	4	220 (100—[illegible]60)	+10 (+10—+[illegible]0)	+10 (+10—+15)	+15 (+10—+17)
Animals with an initial heart rate of [illegible]30—300/min	A	3	300 (290—310)	±0 (—5—+10)	±0 (—10—+5)	±0 (—5—+10)
	B	3	280 (0—300)	+10 (—10—+20)	+10 (0—+[illegible]0)	±0 (0)
	C	1	260 (—)	+10 (+10)	+10 (+10)	+10 (+10)
Animals with an initial heart rate of [illegible]00—[illegible]30/min	A		233 ([illegible]30— 40)	+60 (+ 0)	+40 (+80)	+40 (+60)
	B	4	220 (200—230)	+20 (—20—+60)	+10 (—60—+40)	+5 (—80—+30)
	C	2	235 (230— 40)	+10 (+10)	+15 (+15)	+15 (+15)
Animals with an initial heart rat of 1[illegible]0—200/min	A	5	1 0 (150—190)	+60 (—40—+100)	+30 (—30—+130)	±0 (—30—+60)
	B	1	180 (1 0—[illegible]00)	+35 (—90—+80)	+[illegible]0 (+5—+30)	+[illegible]5 (—5—+30)
	C	1	160 (—)	+10 (+[illegible]0)	— —	— —

Decreases were observed in three cases. In group B the greatest changes were +56 and —38 per cent decreases in stroke volume occurred at some moment during the experimental period in 9 cases out of 11 In group C the stroke volume either decreased or remained unchanged.

The changes in central blood volume (Fig 7) during hypoxia paralleled the changes in cardiac output and stroke volume Thus, the central blood volume increased 21 to 25 per cent in group A ($p < 0.01$) and 11 to 14 per cent ($p < 0.05$) in group B but decrease about 8 per cent ($p < 0.05$) in group C Th changes in groups A and C differed almos significantly ($p < 0.05$) The individua changes in central blood volume were abou the same as those in stroke volume Increase up to 79 per cent occurred in seven and de creases up to 13 per cent in three of the ten animals of group A Increases up to 62 per cent occurred in six and decreases of at most 16 per cent in five of the 11 animals of group B In group C decreases were the rule

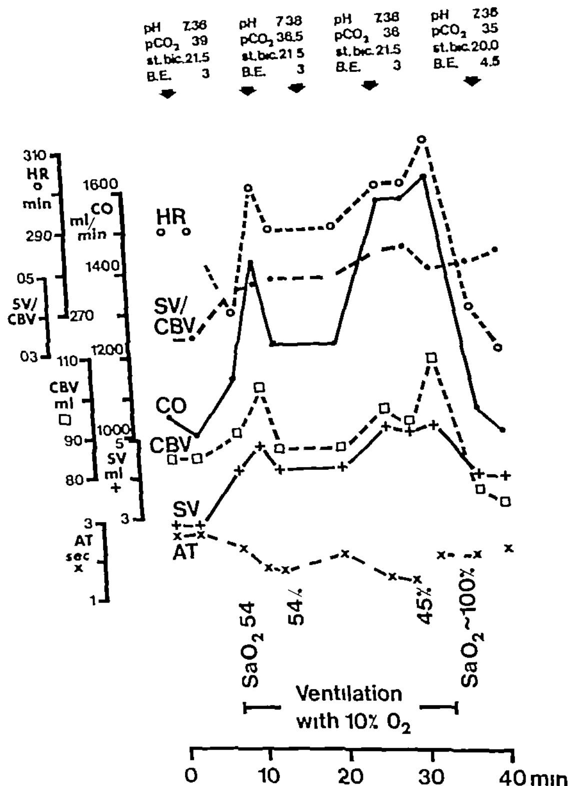


Fig 10 The cardiovascular pattern during hypoxia in nine-day old lamb weighing 2.7 kg to hich 200 mg of chloralose was administered and which was ventilated with a respirator. The lamb did not develop severe acidosis. During the hypoxia, CO increased clearly as consequence f an increased SV. HR dropped at first, but increased later. The changes in AT

mask hyperventilated and their pCO_2 values decreased ($p < 0.001$) (Table VII) Owing to oxygen deficiency and elevated lactic acid concentration the standard bicarbonate level and base excess decreased significantly ($p < 0.001$) The decreases of standard bicarbonate and base excess were roughly the same in groups A B and C The changes in pCO and standard bicarbonate counteracted each other so that pH of the arterial blood did not change

Seven lambs were ventilated with a respirator during hypoxia to prevent hypocapnia. In five of these acid base values were determined both before and during the experiment (Table VIII) The decrease in pCO_2 was not significant but the standard bicarbonate level decreased as it did in lambs that hyperventilated freely ($p < 0.01$)

Effect of chloralose on the cardiovascular response to hypoxia

Because a part of the lambs of the hypoxia group were anesthetized with chloralose the results for lambs that were anesthetized and lambs that were not will be compared The changes in cardiac output and heart rate resulting from hypoxia are shown in Fig 9 It will be seen that the mean changes in cardiac output and heart rate during hypoxia did not differ significantly in the two groups.

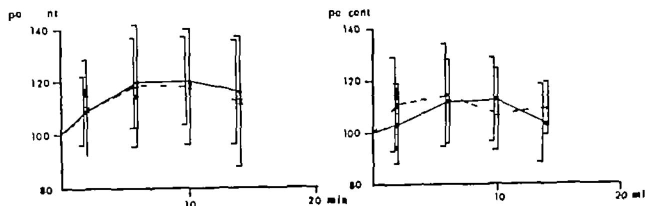


Fig 9 Comparison of cardiac output (left) and heart ate (right) responses during hypoxia in 9 unan sthetized lambs ( ) nd in 10 lan bs subjected to hloralose a esthesia (×) The ertical lines represent 2 × S.D

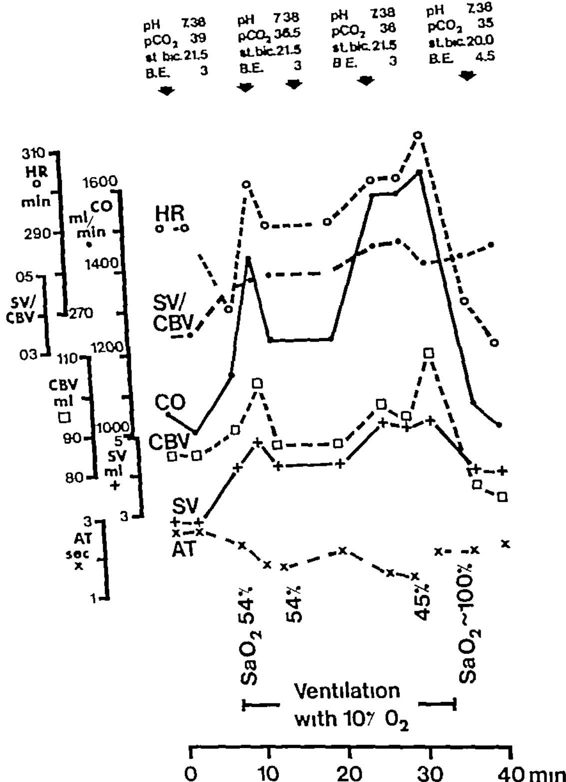


Fig. 10 The cardiovascular pattern during hypoxia in a nine day old lamb weighing 3.7 kg to which 200 mg of chloralose was administered and which was ventilated with a respirator. The lamb did not develop severe acidosis. During the hypoxia, CO increased clearly as a consequence of an increased SV. HR dropped at first, but increased later. The changes in AT, SV/CBV and CBV are not typical for the whole series. pCO_2 decreased slightly and a slight decrease in B.E. indicated accumulation of fixed acid.

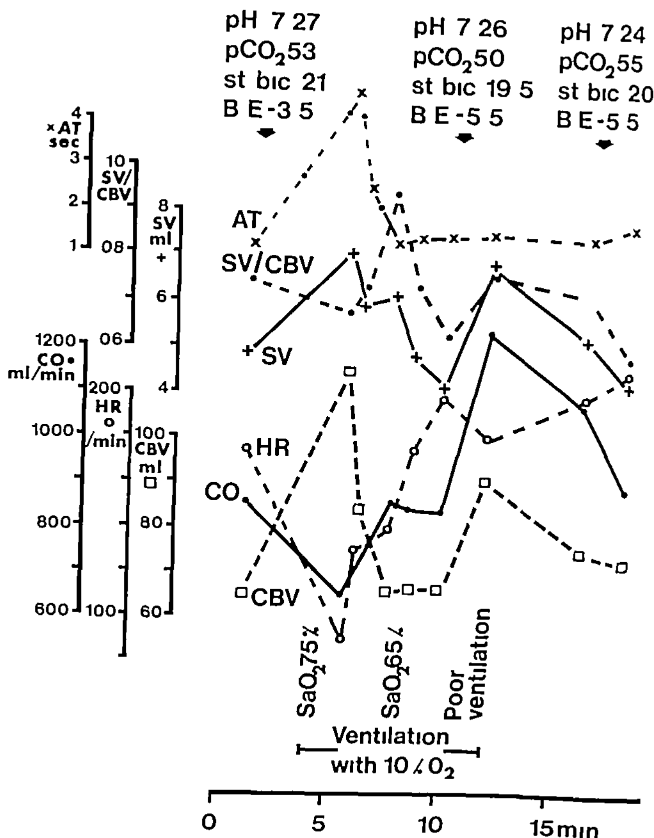


Fig 11 ... during hypo ... two-... -old ... weighing 3 0 kg that was not anesthetized. The ... breathed poorly before the hypoxia. The respiration improved ... while after the induction of hypo... as indicated by increased pCO_2 values. At the beginning of the hypoxic period, ... developed and the cardiac output decreased. At the same time CBV increased and AT ... considerably. A typical hypoxia pattern with increased CO, SV and CBV was observed at the ... The return to the initial ... was abnormally low.

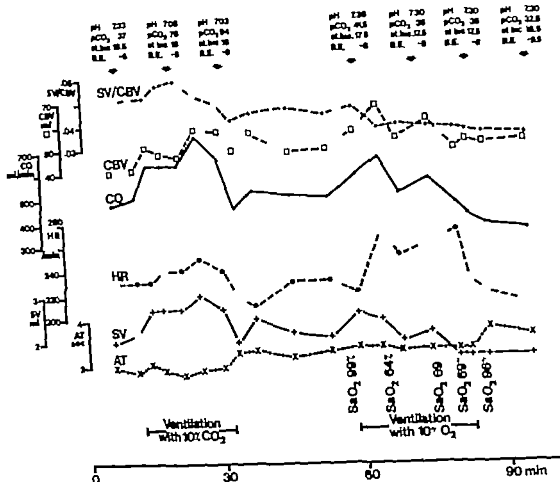


Fig 12 A two-day-old lamb weighing 2.7 kg that was anesthetized with 90 mg of chloralose. Metabolic acidosis had developed before the experiments. A respirator was used although the ventilation was sufficient. Hypercapnia On ventilation with 10 per cent CO_2 a typical pattern appeared. CO increased and this was more a result of increased SV than of increased HR. Also CBV increased, but AT remained practically unchanged. The values reverted to the initial levels when the supply of CO_2 was discontinued.
Hypoxia Cardiac output increased at first due to an increase in HR. Later CO decreased, a change often observed in metabolic acidosis of this degree. The changes in CBV paralleled those of CO.

ARTERIAL HYPOXIA IN SHEEP

Arterial hypoxia was induced in six sheep to obtain data for comparison with the data for the lambs. In these experiments it was more difficult to induce levels of arterial oxygen saturation as low as those in the lambs. The oxygen saturation ranged from 70 to 85 per cent (mean 8 per cent) in these experiments with the sheep. Hence the results for sheep and neonatal lambs are not directly comparable.

Fig 13 shows the changes in different circulatory parameters during hypoxia as percentages of the initial levels. In these calculations, the initial relative S.D was taken to be 10 per cent for cardiac output stroke volume, central blood volume and the ratio SV/CBV and 5 per cent for heart rate. The mean cardiac output increased by 65 per cent ($p < 0.001$) and remained at the elevated level for at least 4 minutes. The large variation of the values of this parameter was

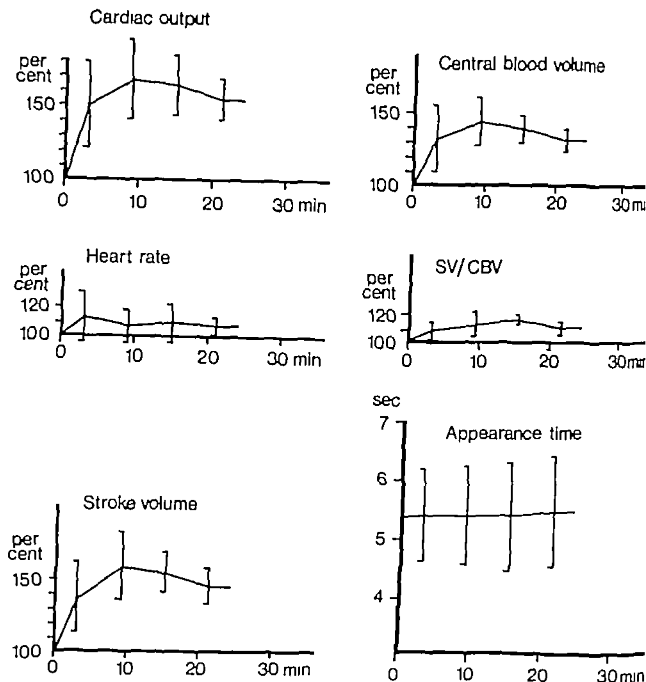


Fig 13. Changes in cardiac output, heart rate, stroke volume, central blood volume, ratio SV/CBV (in per cent) and appearance time (in seconds) as functions of time during hypoxia in sheep from 6 to 1 mo th old. The lengths of the vertical lines are equal to 2 × S.D. (n = 6)

probably due to differences in arterial oxygen saturation. The greatest increase, to 245 per cent of the initial level was recorded at an arterial oxygen saturation of 75 per cent (Fig 14). The smallest increase, to 140 per cent, occurred at an arterial oxygen saturation of 82 per cent. In two experiments which lasted more than 30 minutes, the cardiac output remained elevated throughout the hypoxia period.

The heart rate rose only 5 to 10 per cent during hypoxia ($p < 0.05$).

The changes in stroke volume were responsible for the changes in cardiac output. The mean increase in stroke volume was 56 per cent ($p < 0.001$).

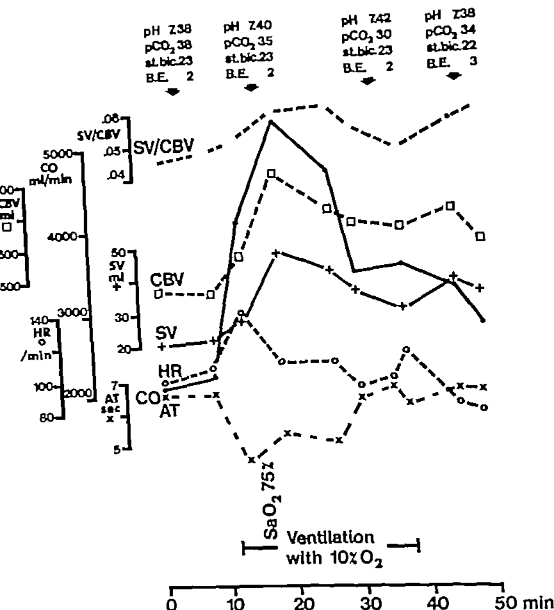


Fig. 14. Data for sheep 13 months old, eight 33 kg, under Nembutal sedation. During hypoxia with an arterial oxygen saturation of 75 per cent, CO and SV increased, but HR did not rise markedly. Also CBV increased, but despite this AT decreased clearly. Owing to hyperventilation, pCO_2 decreased.

The central blood volume changed in parallel with the cardiac output and stroke volume. It increased 4[illegible] per cent on average during the hypoxia ($p < 0.001$). The relative increase in CBV was less than the relative increase in cardiac output. Thus, a decrease in appearance time should have occurred, but the mean appearance time did not change although the individual appearance times varied greatly. A considerable decrease in appearance time occurred in the sheep to which the case report in Fig. 14 refers.

The ratio SV/CBV did not vary as much in the sheep as in the neonatal lambs. The ratio

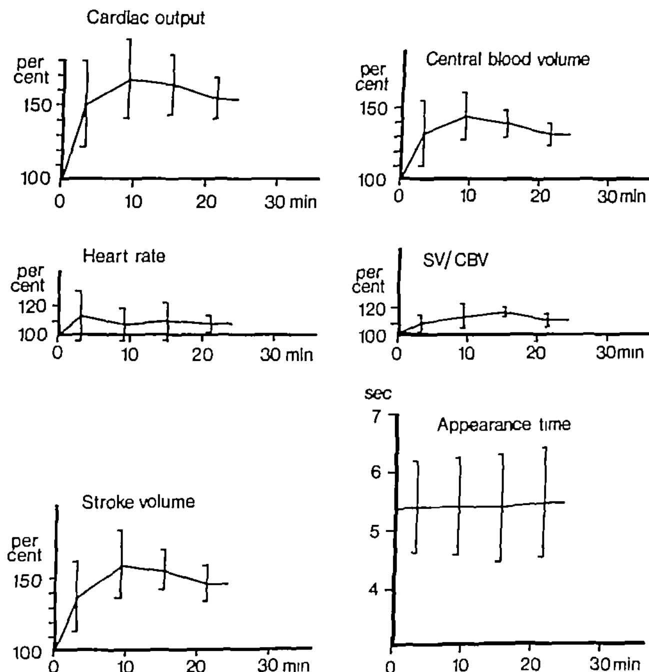


Fig 13. Changes in cardia output heart rate, stroke olume, central blood lume, ratio SV/CBV (in per cent) and appearance tim (in seconds) as functions of time during hypoxia in sheep from 0 to 12 months old. The lengths f the ertical lines are equal to 2 × S.D (n = 6)

probably due to differences in arterial oxygen saturation The greatest increase to 245 per cent of the initial level, was recorded at an arterial oxygen saturation of 75 per cent (Fig 14) The smallest increase, to 140 per cent, occurred at an arterial oxygen saturation of 82 per cent In two experiments which lasted more than 30 minutes, the cardiac output remained elevated throughout the hypoxia period.

The heart rate rose only 5 to 10 per cent during hypoxia ($p < 0.05$)

The changes in stroke volume were responsible for the changes in cardiac output. The mean increase in stroke volume was 56 per cent ($p < 0.001$)

TABLE IX. Acid-base values ± S.D. of lambs before (11 determinations) and during (14 determinations) hypercapnia experiments.

	Before the experiment	During the experiment
Actual pH	7.34 ± 0.003	7.17 ± 0.005
Actual pCO_2 (mmHg)	41.9 ± 1.4	76.0 ± 18.0
St. bicarbonate (meq/L)	21.1 ± 4.2	20.7 ± 3.5

TABLE X. Heart rate changes (beats per minute) in neonatal lambs during hypercapnia.

	Number of cases	Mean initial heart rate (range)	Mean change in heart rate from initial level at 6 min. (max. variations during 0—6 min.)	Mean increase of heart rate from initial level at 1 min. (max. variations during 0—1 min.)
The whole series	14	230 (160—290)	+30 (—00—+70)	+30 (—30—+70)
Animals with initial heart rates of 250—300/min.	4	273 (250—290)	—10 (—90—+20)	±0 (—20—+10)
Animals with initial heart rates of 200—230/min.	3	220 (200—230)	+40 (+10—+70)	+40 (0—+50)
Animals with initial heart rates of 130—200 min.	5	180 (160—190)	+30 (—20—+70)	+60 (+20—+70)

Cardiovascular changes

Different degrees of metabolic acidosis caused large differences in the initial cardiac outputs. In lambs with B.E. of 0 to —3 meq/l, the initial cardiac output ranged from 230 to 360 ml/min/kg. In a lamb with a B.E. of —11 meq/l it was 190 ml/min/kg and in another lamb with a B.E. —18 meq/l it was 80 ml/min/kg. Because of these large variations, the changes in the circulatory parameters as percentages of the initial levels were calculated assuming an initial S.D. of 10 per cent for cardiac output, stroke volume, CBV and the ratio SV/CBV and 5 per cent for heart rate.

Fig. 15 shows the circulatory changes in the lambs during hypercapnia. The cardiac output had increased 27 per cent on average ($p < 0.001$) when the experiment had lasted 10 minutes. The largest increases were up to 60 per cent of the initial level.

In two cases, initial decreases of 5 and 10 per cent occurred. Fig. 15 shows that an increase in heart rate of 13 per cent ($p < 0.001$) and an increase in stroke volume of 12 per

increased up to 12 per cent in the sheep the mean increase was significant ($p < 0.01$)

No signs of shunts were observed in the sheep

The acid base values showed a decrease of arterial pCO_2 from 42 mmHg (range 37—45 mmHg) to 35 mmHg (range 30—38 mmHg) during hypoxia The mean change in standard bicarbonate level (from 24.5 to 24.0 meq./l.) was not significant The pH rose from a mean value of 7.39 to a mean value of 7.44 during hypoxia

HYPERCAPNIA IN NEONATAL LAMBS

The changes in arterial acid base balance in lambs given air containing 10 per cent carbon dioxide are presented in Table IX. The arterial pCO_2 levels were normal before the experiments. In contrast the degree of metabolic acidosis varied greatly there were eight lambs with B.E. of 0 to —5 meq./l. four lambs with B.E. of —5 to —10 meq./l. and two lambs with B.E. of less than —10 meq./l.

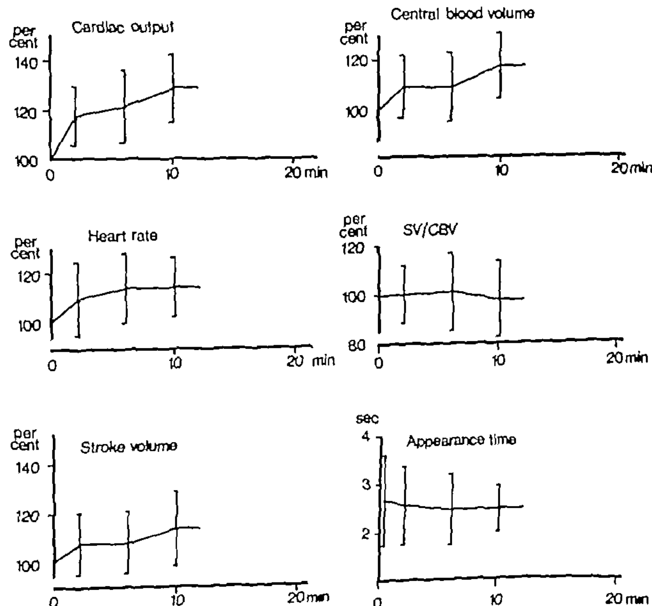


Fig 15 Ch nges i ardia output heart rat st oke lume central blood ol me rat SV/CBV (i pe) and) pearan e time (in seco) as functions f time in neonat l lambs du i g hypercap ia The length f t rt cal lines re S.D (= 14)

TABLE IX. Acid-base values ± S.D. of lambs before (11 determinations) and during (14 determinations) hypercapnia experiments.

	Before the experiment	During the experiment
Actual pH	7.34 ± 0.003	7.17 ± 0.005
Actual pCO_2 (mmHg)	41.0 ± 1.4	78.0 ± 15.0
St. bicarbonate (meq./l.)	21.1 ± 4.[illegible]	20.7 ± 3.5

TABLE X. Heart rate changes (beats per minute) in neonatal lambs *during hypercapnia.*

	Number of cases	Mean initial heart rate (range)	Mean change in heart rate from initial level at 6 min. (max. variations during 0—6 min.)	Mean increase of heart rate from initial level at 15 min. (max. variations during 6—15 min.)
The whole series	14	220 (160—290)	+30 (—60—+ 0)	+20 (—20—+ 0)
Animals with initial heart rates of 250—300/min.	4	273 (260—290)	—10 (—60—+20)	±0 (—20—+10)
Animals with initial heart rates of 200—250 min.	3	230 (200—230)	+40 (+10—+70)	+40 (0—+50)
Animals with initial heart rates of 150—200 min.	5	180 (160—190)	+50 (—20—+70)	+50 (+20—+70)

Cardiovascular changes

Different degrees of metabolic acidosis caused large differences in the initial cardiac outputs. In lambs with B.E. of 0 to —5 meq./l., the initial cardiac output ranged from 230 to 360 ml/min/kg; in a lamb with a B.E. of —11 meq./l. it was 120 ml/min/kg and in another lamb with a B.E. —18 meq./L, it was 80 ml/min/kg. Because of these large variations, the changes in the circulatory parameters as percentages of the initial levels were calculated assuming an initial S.D. of 10 per cent for cardiac output, stroke volume, CBV and the ratio SV/CBV and 5 per cent for heart rate.

Fig. 15 shows the circulatory changes in the lambs during hypercapnia. The cardiac output had increased 27 per cent on average ($p < 0.001$) when the experiment had lasted 10 minutes. The largest increases were up to 60 per cent of the initial level.

In two cases, initial decreases of 5 and 10 per cent occurred. Fig. 15 shows that an increase in heart rate of 13 per cent ($p < 0.001$) and an increase in stroke volume of 1 per

cent ($p < 0.01$) had the same effect on the cardiac output response.

The initial heart rate seemed to determine its response during hypercapnia (Table X). When the initial heart rate was high (> 250/min) the rate increased only slightly to a maximum value of 300 per minute in two animals, and decreased in two animals. When the initial heart rate was from 150 to 250 per minute, an increase usually occurred.

The stroke volume increased 12 per cent on average during 10 minutes of hypercapnia ($p < 0.01$). Large variations occurred: the largest increase was 50 per cent and in three cases the stroke volume decreased 5 to 25 per cent.

The central blood volume changed in parallel with the stroke volume. The mean increase in central blood volume at the tenth minute of the experiment was 16 per cent ($p < 0.001$).

As could be expected from the parallel variations of SV and CBV the mean ratio SV/CBV did not change at all. Individual variations up to ± 35 per cent occurred in this parameter.

The dye appearance time also varied considerably in different animals during hypercapnia: both increases and decreases were observed, but the mean change was an insignificant decrease.

There were signs of small right-to-left shunts in the dye dilution curves of the lambs during hypercapnia. The curves for one lamb (see Fig. 17) exhibited a large right-to-left shunt during the hypercapnia period.

Fig. 12 shows a typical cardiovascular pattern during hypercapnia for a lamb with moderate metabolic acidosis. Among the animals there were two interesting cases. Fig. 17 shows a total A—V block which developed during hypercapnia in a lamb with severe metabolic acidosis. The heart rhythm reverted to normal when the supply of air containing 10 per cent carbon dioxide was replaced with air. Fig. 18 presents a case with a probable sinus bradycardia and its response to hypercapnia.

Effects of chloralose anesthesia

As mentioned before metabolic acidosis developed generally more rapidly in lambs subjected to chloralose anesthesia than in unanesthetized lambs. Chloralose was administered to eight lambs of the hypercapnia series. The two lambs with B.E. of less than —10 meq./l. were anesthetized. Chloralose seems to depress the cardiac output and heart rate responses ($p < 0.05$) during hypercapnia (Fig. 16).

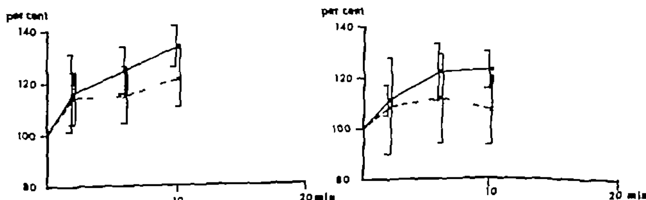


Fig. 16. Mean changes in cardiac output (left) and heart rate (right) during hypercapnia in six unanesthetized lambs ( ) and eight lambs subjected to chloralose anesthesia (X). The lengths of the vertical lines are equal to ± S.D.

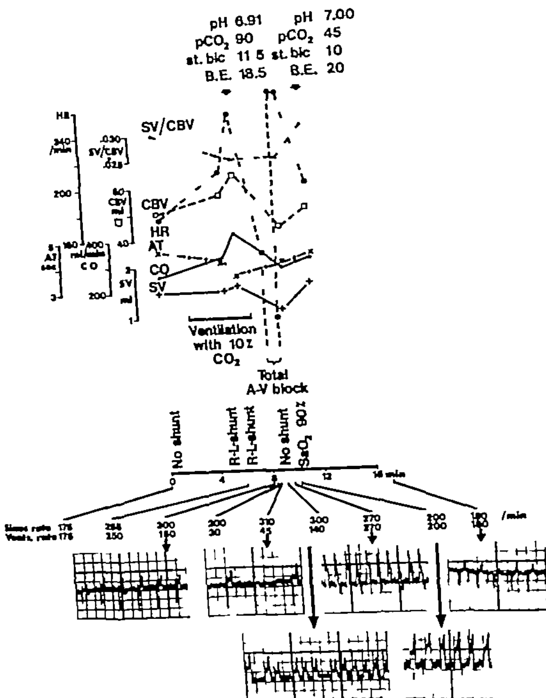


Fig 17. Total A—V block in a lamb 40 hours old, weight 3.3 kg, under chloralose anesthesia. The lamb was not anesthetized at first but as it was observed to shiver, 160 mg of chloralose was administered. As this caused respiratory arrest, ventilation with a respirator was begun. As a result of inadequate ventilation, combined respiratory and metabolic acidosis developed. During the hypercapnia experiment, HR and probably CO increased. After 5 minutes, the ventricular rate suddenly slowed down to 30 beats per minute but the auricular rate continued to be 200 beats per minute. At that time ventilation with 10 per cent CO_2 was discontinued and extrathoracic heart massage was performed for a few seconds, after which an immediate improvement was seen in the ECG. In spite of the normalized heart rate, ST-T changes suggesting myocardial damage were seen. The ECG reverted to the initial normal pattern when nine minutes had elapsed after the block.

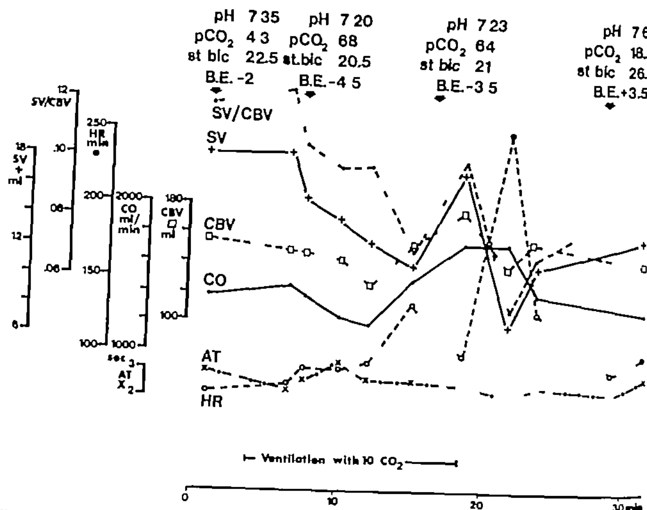


Fig 18. A 14-day-old lamb, weighing 4. kg, not nesthetized. When preparation was begun, the HR of the lamb was abnormally low (from 70 to 90 per minut) J dging from FCG records this rhythm arose from the sinus node but because of th poor quality of the ECG the possibility of a total A—V block could not be xcluded. During the hypercapnia period, the cardio ascula patt rn was completely atypical. At the 12th to 14th minute of the experiment CO increased slightly Howeve aft the e perimental period when the lamb was breathing air a pronounced tachycardia developed and remained at the high level seen in late hypercapnia. This period of tachycardia ceased within 30 seconds and the earlier low HR returned. During these changes the form of the QRS comple es remained essentially unchanged, indicati g uricular or t least nodal pacing of the heart.

HYPERCAPNIA IN SHEEP

Hypercapnia was induced in two sheep 12 months old. In both sheep the acid base values were almost normal before the experiment (pH 7.39 and 7 41 pCO 37 and 39 mmHg standard bicarbonate 23 and 24 meq /l and B E —2 and —3 meq /L) During hyper capnia, the actual pCO values increased to 74 and 82 mmHg an l the pH values decreased to 7 21 and 7 18 respectively in the two sheep

The cardiovascular changes observed in these sheep are presented in Fig 19 The changes in cardiac output stroke volume and central blood volume resemble those observed in the neonatal lambs. The heart rate d creased in one sheep and remained unchange in the other

METABOLIC ACIDOSIS IN NEONATAL LAMBS

The cause of the metabolic acidosis observed in many lambs during this study is somewhat problematic. In some animals it clearly de-

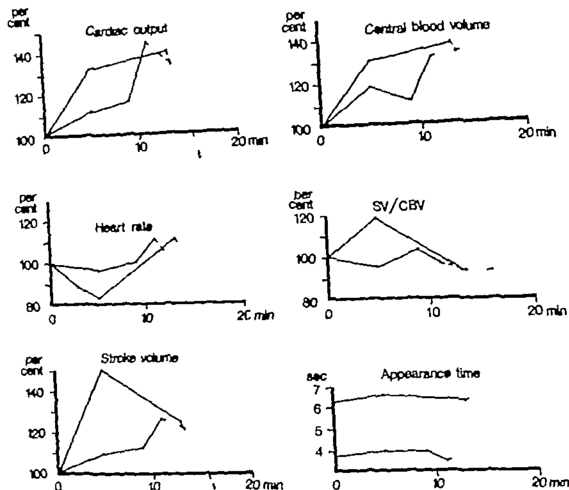


Fig. 18. Changes in cardiac output, heart rate, stroke volume, central blood volume, ratio SV/CBV (in per cent) and appearance time (in seconds) in two 18-month old sheep during hypercapnia. The solid lines refer to the experimental period and the broken lines to the air-breathing period.

eloped during experimental hypoxia (Tables VII and VIII) but it seemed to develop *spontaneously in many animals*. The lambs with metabolic acidosis were younger on average than the other lambs (Table III). The lambs were often distressed when placed on the table: they breathed quickly, shivered *and were restless. Administration of chloralose* clearly favored the development of metabolic acidosis. Eight of the nine neonatal lambs were anesthetized with chloralose. After its administration, the lambs often began to breathe rapidly and shallowly but no clear signs of arterial hypoxia were *detected. There* were also other lambs in which metabolic acidosis developed, but only in these nine animals were the cardiovascular parameters and acid-base values measured simultaneously. Only lambs with pCO of less than 45 mmHg were accepted for this analysis.

The progressive variation of the acid-base values in the nine lambs is presented in Table XI. The values are grouped into initial normal values (9 determinations), values when the B.E. was from —6 to —1 (9 determinations) and values when the B.E. was from —1⁰ to

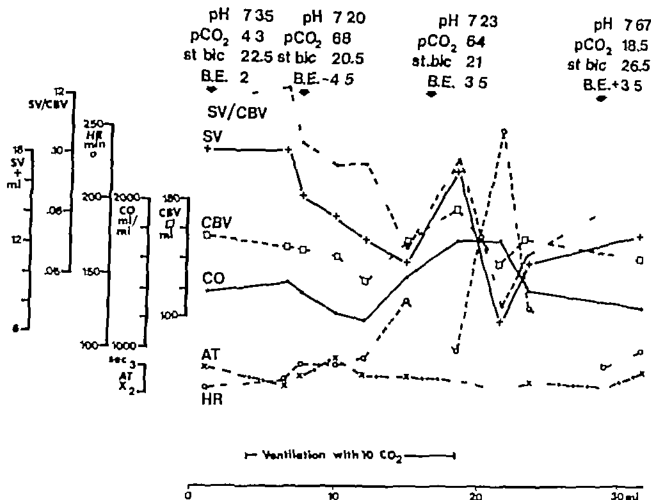


Fig 18. A 14-day-old lamb, weighing 4. kg, not anesthetized. When preparation was begun, the HR of the lamb was abnormally low (from 70 to 90 per minute). Judging from ECG records, this rhythm arose from the sinus node but because of the poor quality of the ECG the possibility of total A—V block could not be excluded. During the hypercapnia period the cardiovascular pattern was completely typical. At the 1 th *to 14th min to of the experiment CO increased slightly. However after the experimental period when the lamb* was breathing air a pronounced tachycardia developed and remained at the high level seen in late hypercapnia. This period of tachycardia ceased within 30 seconds and the earlier low HR returned. During these changes the form of the QRS complexes remained essentially unchanged, indicating auricular or at least nodal pacing of the heart

HYPERCAPNIA IN SHEEP

Hypercapnia was induced in two sheep 12 months old. In both sheep the acid base values were almost normal before the experiment (pH 7 39 and 7 41, pCO_2 37 and 39 mmHg, standard bicarbonate 23 and 24 meq/l and B E —2 and —3 meq/l). During hypercapnia the actual pCO_2 values increased to 74 and 82 mmHg and the pH values decreased to 7 21 and 7 18 respectively in the two sheep.

The cardiovascular changes observed in these sheep are presented in Fig 19. The changes in cardiac output, stroke volume and central blood volume resemble those observed in the neonatal lambs. The heart rate decreased in one sheep and remained unchanged in the other.

METABOLIC ACIDOSIS IN NEONATAL LAMBS

The cause of the metabolic acidosis observed in many lambs during this study is somewhat problematic. In some animals it clearly de-

TABLE XI. Acid-base values (means and ranges) in lambs with developing metabolic acidosis. The numbers of determinations are given in parentheses in the captions.

	Initial values (9)	Lambs with B.E. of −6 to −12 (9)	Lambs with B.E. of −12 to −20 (3)
Actual pH	7.37 (7.33—7.42)	7.21 (7.29—7.26)	7.14 (6.9—7.21)
Actual pCO_2 (mmHg)	41 (38—45)	34 (30—38)	30 (20—45)
St. bicarbonate (meq./l.)	23.1 (23—24)	17.1 (15—19.5)	13.0 (10—16)
B.E. (meq./l.)	−1 (0 — −2.5)	−9 (−6 — −12)	−16 (−13 — −20)

almost entirely by the decrease in stroke volume.

The changes in central blood volume were not so marked as those in the above parameters. It decreased by 18 per cent when the B.E. decreased by 10 meq./l. ($p < 0.01$). In two lambs an increase occurred. The ratio SV/CBV was found to decrease by 23 per cent for a decrease of 10 meq./l. in B.E. ($p < 0.001$). As may be expected from the relatively small decrease in CBV in comparison with that in cardiac output, the dye appearance time increased clearly as metabolic acidosis developed. The increase was 1.2 seconds for a decrease of 10 meq./l. in B.E. ($p < 0.001$).

No signs of fetal shunts were present in dye dilution curves of the lambs of this series. It was, however, impossible to decide with certainty whether a left-to-right shunt was present or not. This difficulty was due to the slow descent of the dye dilution curve when the cardiac output was low.

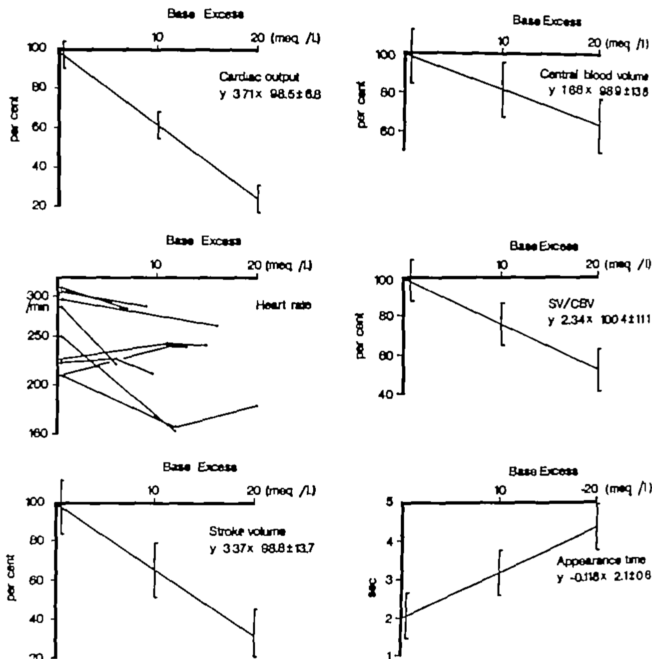


Fig 20 Cardia output heart rate stroke volume, central blood olume ratio SV/CBV d appearance time as functi ns of base excess (n = 9) Th lengths f the v rtical lines are equal to × S.D

—20 meq/l (5 determinations) With decreasing standard bicarbonate, the pH decrease seems to have been compensated for initially by a decrease in arterial pCO As the metabolic acidosis progressed the pCO no longer decreased and the net effect was a lowered pH.

Fig 20 presents the changes in the circulatory parameters in relation to the B.E The cardiac output decreased by 39 per cent for a decrease of 10 meq/l in B.E ($p < 0.001$) The heart rate showed a more variable pattern. In most cases it decreased but in three cases it remained unchanged or increased The stroke volume definitely decreased the decrease being 35 per cent for a decrease of 10 meq/l in B.E ($p < 0.001$) The decrease in cardiac output was caused

TABLE XI. Acid-base values (means and ranges) in lambs with developing metabolic acidosis. The numbers of determinations are given in parentheses in the captions.

	Initial values (9)	Lambs with B.E. of −6 to −12 (9)	Lambs with B.E. of −13 to −20 (5)
Actual pH	7.37 (7.33—7.42)	7.31 (7.29—7.36)	7.14 (6.9—7.31)
Actual pCO_2 (mmHg)	41 (35—43)	34 (30—35)	34 (30—45)
St. bicarbonate (meq./l.)	23.1 (23—24)	17.1 (15—19.5)	13.0 (10—16)
B.E. (meq./l.)	−1 (0 — −2.5)	−9 (−6 — −12)	−16 (−13 — −20)

almost entirely by the decrease in stroke volume.

The changes in central blood volume were not so marked as those in the above parameters. It decreased by 18 per cent when the B.E. decreased by 10 meq./l. ($p < 0.01$). In two lambs an increase occurred. The ratio SV/CBV was found to decrease by 23 per cent for a decrease of 10 meq./l. in B.E. ($p < 0.001$). As may be expected from the relatively small decrease in CBV in comparison with that in cardiac output, the dye appearance time increased clearly as metabolic acidosis developed. The increase was 1.2 seconds for a decrease of 10 meq./l. in B.E. ($p < 0.001$).

No signs of fetal shunts were present in dye dilution curves of the lambs of this series. It was, however, impossible to decide with certainty whether a left-to-right shunt was present or not. This difficulty was due to the slow descent of the dye dilution curve when the cardiac output was low.

Discussion

METHODS

Chloralose anesthesia

Anesthesia in experimental animals is always a compromise and is used when one wishes to avoid larger disturbances than the anesthetic causes. The decision to use it or not depends on what functions of the circulation are to be studied and how much anesthesia affects these functions.

Korner (73) stressed the importance of not using anesthesia in studies of the effects of experimental hypoxia in rabbits because of the large variations in circulatory response caused by anesthesia. On the other hand, avoidance of anesthesia may have the disadvantage that anxiety reactions arise during distressing conditions. It has been shown that anxiety may increase the cardiac output by 35 per cent (54).

Chloralose was used as anesthetic in the present study in the doses recommended by Cross *et al* (26). Massive pulmonary edema occurred once and sudden death occurred twice in lambs anesthetized with these doses. For this reason, chloralose was administered in the latter part of the study only to lambs that were observed to shiver and when tracheotomy was considered necessary.

In general, the chloralose administration promoted the development of metabolic acidosis and caused tachycardia. It may also have had a depressing effect on the cardiac response to hypercapnia (Fig 16) but no effect on the cardiac response to hypoxia was found.

The unanesthetized lambs remained surprisingly calm during the hypoxia and hypercapnia experiments. Only increased respiratory effort was observed constantly but the animals were not usually restless. The anesthesia hence appears not to be necessary in experiments of the type performed on neonatal lambs in the present study if procedures like tracheotomy do not require it.

Preparation and experiments

The procedures requiring surgery were done so as to be as little traumatic as possible. According to Korner (73) catheterization of major vessels should be avoided in hypoxia experiments. The femoral artery and superficial jugular vein were the only vessels catheterized in this study. These procedures hardly influenced the circulation significantly.

The warming plate on which the lambs were laid appeared to be necessary. If it was not used, the body temperatures of the lambs tended to fall. When it was used the animals maintained a normal temperature of 39 to 41 C.

The total blood volume of about 15 ml removed during the experiments was at most 9 per cent of the assumed total blood volume in the smallest lambs. The blood losses were replaced with saline or in some cases, with blood from the ewe. No blood incompatibility was observed between the lambs and their own ewes in a simple cross-matching test.

During experiments lasting 3 to 4 hours,

an actual blood loss was still a possibility This may have influenced the results concerning the effects of metabolic acidosis on the circulation of neonatal lambs.

Measurements

At present the dye dilution method seems to be the method of choice for circulatory studies in newborn infants and lambs, because of its small disturbing effects on the cardiovascular functions. The Fick principle is not applicable in experiments in which a steady state may not be obtained (43, 78 88, 69 134) Flow meters which permit simultaneous measurements of flow through different vessels mostly require thoracotomy which causes cardiac shrinkage (106) The pulse-contour method which measures every stroke volume separately is not yet accurate enough, but probably will be useful for flow measurements in the future (130)

The blood withdrawn through the cuvette was from 10 to 15 ml in the experiments with the lambs. If the lamb is assumed to have a blood volume of 80 ml/kg, the removed blood volume, which was returned, was 9 per cent of the total blood volume of the smallest lamb (1 kg) A blood loss of this magnitude has been found by Wallgren *et al.* (127) to decrease cardiac output and stroke volume and to increase the peripheral resistance in newborn infants. Therefore, low values of these parameters may have been recorded for the smallest lambs.

The fetal shunts which occurred in the youngest lambs were somewhat disturbing as they made calculations from dye curves difficult Therefore lambs younger than 36 hours were not used. In older lambs signs of shunts were sometimes observed but not constantly Curves which indicated large shunts were rejected The shunt flows were not calculated because the study was mainly concerned with cardiac function.

The self-designed dye-dilution apparatus was found to yield results of satisfactory accuracy (Figs. 1 and ?) The test results for the artificial flow system were good, but the accuracy was not as good in the experiments with lambs owing to less accurate calibration when blood than when water was the liquid. As concluded from successive measurements of cardiac output in steady state conditions, the maximum errors were up to ± 15 per cent. Mostly successive determinations agreed within ± 10 per cent. The accuracy of this apparatus seems thus to be equal to that of commercial apparatus. A disadvantage f the apparatus was that it required constant watching therefore, other valuable measurements, such as those of arterial and other pressures, could not be done concurrently

Temperature measurement with a rectal electrode is not so accurate as with an esophageal electrode because the former electrode follows the temperature of body core more slowly than the esophageal electrode. The use of an esophageal electrode in unanesthetized lambs was unsuccessful because the lambs became restless and vomited easily In the experiments with lambs the temperature range was narrow as no quick changes occurred owing to the warming plate. Therefore the measurement of rectal temperature may be considered to have been satisfactory

The micro method developed by Siggaard Andersen *et al.* (113) and Siggaard Andersen and Engel (114) for measuring acid-base values is in common clinical use and was therefore applied in this study The measurement of standard bicarbonate makes it possible to obtain direct data on the content of fixed acids without any *influence* of the partial pressure of carbon dioxide. The standard deviations of the method given by the authors are 0.006 units for pH, per cent for pCO_2, and 0.3 meq./l. for standard bicarbonate when the values are in the normal ranges (113)

Discussion

METHODS

Chloralose anesthesia

Anesthesia in experimental animals is always a compromise and is used when one wishes to avoid larger disturbances than the anesthetic causes. The decision to use it or not depends on what functions of the circulation are to be studied and how much anesthesia affects these functions.

Korner (73) stressed the importance of not using anesthesia in studies of the effects of experimental hypoxia in rabbits because of the large variations in circulatory response caused by anesthesia. On the other hand, avoidance of anesthesia may have the disadvantage that anxiety reactions arise during distressing conditions. It has been shown that anxiety may increase the cardiac output by 35 per cent (54)

Chloralose was used as anesthetic in the present study in the doses recommended by Cross *et al* (26) Massive pulmonary edema occurred once and sudden death occurred twice in lambs anesthetized with these doses. For this reason chloralose was administered in the latter part of the study only to lambs that were observed to shiver and when tracheotomy was considered necessary

In general the chloralose administration promoted the development of metabolic acidosis and caused tachycardia It may also have had a depressing effect on the cardiac response to hypercapnia (Fig 16) but no effect on the cardiac response to hypoxia was found.

The unanesthetized lambs remained surprisingly calm during the hypoxia and hypercapnia experiments. Only increased respiratory effort was observed constantly but the animals were not usually restless. The anesthesia hence appears not to be necessary in experiments of the type performed on neonatal lambs in the present study if procedures like tracheotomy do not require it.

Preparation and experiments

The procedures requiring surgery were done so as to be as little traumatic as possible. According to Korner (73) catheterization of major vessels should be avoided in hypoxia experiments. The femoral artery and superficial jugular vein were the only vessels catheterized in this study These procedures hardly influenced the circulation significantly

The warming plate on which the lambs were laid appeared to be necessary If it was not used the body temperatures of the lambs tended to fall. When it was used, the animals maintained a normal temperature of 39 to 41°C

The total blood volume of about 15 ml removed during the experiments was at most 9 per cent of the assumed total blood volume in the smallest lambs. The blood losses were replaced with saline or in some cases, with blood from the ewe. No blood incompatibility was observed between the lambs and their own ewes in a simple cross-matching test.

During experiments lasting 3 to 4 hours,

bilities are lacking in the literature. As a result of the increased heart rate a decrease in stroke volume, and consequently also in the ratio SV/CBV occurred in the anesthetized lambs. The cardiac output and CBV were not significantly influenced by the drug. This agrees with the results of Wiggers (133) who found no change in the cardiac output of adult dogs after administration of chloralose.

The present data do not allow one to draw any conclusions about fetal shunts, because animals with large shunts were rejected. In normal steady state conditions, the lambs more than 36 hours old rarely showed signs of shunts, but patent arterial ducts were observed at autopsy in lambs without any signs of shunts in the dye curves.

EFFECTS OF ARTERIAL HYPOXIA

When the literature on hypoxia ten to forty years old is reviewed, greatly varying results and statements are found. This variability appears to have been due to differences in experimental methods, conditions and animals.

The results obtained in this study differ somewhat from the results of earlier studies on neonatal lambs. Cross *et al.* (26) and Stahlman *et al.* (117) did not find any significant change in cardiac output in neonatal lambs during hypoxia whereas a significant increase in cardiac output was observed in this study when the acid base conditions were normal. Cross *et al.* applied the Fick principle; this may have led to the measurement of unchanged cardiac outputs as discussed in the section on methods. Metabolic acidosis may have developed in the lambs due to progressive hypoxia during the long experimental periods they employed. Complete data on the acid-base balances were not given, but lactic acid concentrations up to 82 mg per 100 ml were reported. This corresponds to almost 10 meq/L, and according to the present results, the cardiac output does not increase during hypoxia when this degree of metabolic acidosis prevails. The difference between the present results and those of Stahlman *et al.* (117) cannot be explained, because the only pronounced difference was that they used eight per cent oxygen and 10 per cent oxygen was supplied to the lambs in this study.

The change in cardiac output was poorly correlated with the arterial oxygen saturation level when acidosis was disregarded (Fig. 6). According to Korner (73) the increase in cardiac output is correlated with the degree of hypoxia in tissues. As evidence for this statement, he presented data of different authors which showed that the increase in cardiac output correlates very well with oxygen saturation in mixed venous blood (73). Surprisingly the same correlation was found in man, rabbit and dog.

Although an increase of cardiac output occurred in the lambs during hypoxia when acid-base conditions were normal, the increase was clearly smaller in lambs than in sheep. The cardiac output increased by 31 to 35 per cent in lambs with a mean arterial oxygen saturation of 67 per cent (Fig. 7) whereas the increase was 65 per cent in sheep with a mean arterial oxygen saturation of 76 per cent (Fig. 13). An explanation for the weak response of the heart in newborn during hypoxia may be that the heart is simply working at almost full capacity and is therefore unable to increase its output as much as the adult heart. As mentioned in the literature review neurohumoral regulation is not essential for increased cardiac function during hypoxia in adults. Hence the reason for the weak response of the cardiac output of lambs to hypoxia must be found in the heart itself. It is known that the myocardial enzyme pattern of newborn rats is such that energy production by anaerobic glycolysis is capable of maintaining heart function in asphyxia

BASAL CIRCULATORY VALUES

Measurement of basal conditions in the circulation seems to require normal acid-base values. A decrease of 1 meq/l in B.E. was found to decrease the cardiac output by about four per cent and increased levels of carbon dioxide were found to increase the cardiac output. Therefore, the required normal limits of B.E. were ± 3 meq/l and those for pCO_2 40 ± 5 mmHg.

It was observed that the cardiac output (ml/min. kg) increased by 50 per cent during the first eight days of life and decreased subsequently to adulthood. The cardiac outputs of lambs less than 30 days old were smaller than those reported by Cross *et al.* (26) and even smaller than those reported by Stahlman *et al.* (117). The cardiac output values for the youngest lambs agree well with those observed by Mahon *et al.* (84) for full term fetal lambs and by Assali *et al.* (9) for newborn lambs. As mentioned before the dye dilution method may have given cardiac output values approximately 10 per cent too low for the youngest lambs.

The increase in cardiac output during the first eight days of life appears reasonable because the oxygen consumption per kilogram increases and the oxygen-carrying capacity of the blood decreases during this period (26). The variation of cardiac output in newborn infants during this period has not been measured. It would be expected to increase during the first two weeks of life because the oxygen consumptions of normal and premature infants increase clearly during this period (79, 109). Also the decrease in circulation time in newborn infants during the first three weeks after birth that was observed by Jegier *et al.* (66) may indicate an increasing cardiac output.

The central blood volume has not previously been measured in neonatal lambs. It changed in parallel with the cardiac output. This relationship has been observed also in human adults in which it is maintained during exercise (115). This relationship is not a methodological characteristic of the dye dilution method, because the area below the primary curve from which the cardiac output is determined and the mean transit time change independently. The CBV was a maximum 28 ml/kg at the age of nine days. If the total blood volume were 80 ml/kg the CBV would amount to 35 per cent of the total blood volume. This is close to the value 38 per cent reported for human adults by Hegglin *et al.* (60).

The ratio of CBV to the total blood volume in sheep 12 months old is only 16 per cent if the total blood volume is 80 ml/kg; this percentage is much lower than that observed in adult humans (60).

The distribution of blood apparently changes immediately after birth so that blood is shifted from the peripheral circulation to the intrathoracic space. Subsequently there occurs a shift in the opposite direction. The decrease in the ratio SV/CBV to adulthood possibly indicates that the blood distribution changes within the central circulation so that the blood in the heart is a smaller proportion of the CBV and consequently the SV becomes smaller in comparison with CBV. The large hearts of newborn infants relative to body size agree with these conclusions.

The appearance time did not decrease in lambs after birth as it does in infants (66) but increased linearly with age. It was found that the AT is directly proportional to the ratio of CBV to cardiac output. This is in agreement with the earlier observation that a change in the site of injection in a peripheral or central vein does not alter the circulation time significantly (66).

Chloralose anesthesia was found to cause tachycardia in lambs. The same has been observed in adult dogs (80). The reason for this may be either a sympathomimetic action or inhibition of the vagus nerve by chloralose. Arguments supporting one of these possi

agrees with earlier findings for dogs (11 61 67 89 107 120) Marshall and Shephard (85) claimed that the increased CBV is distributed over the large arteries during exercise. This cannot occur in lambs during hypoxia, because the mean arterial pressure decreases (117) Further aortographies made in our laboratory reveal that the caliber of the aorta remains unchanged or decreases slightly during hypoxia. Thus, the most probable space available for the increased CBV is the pulmonary vascular bed and the heart. This conclusion is not, however in agreement with the finding of Stahlman *et al.* (117) that the pulmonary blood volume measured by the slope method and the volume calculated from pulmonary transit time decrease during hypoxia in newborn lambs.

The ratio SV/CBV was calculated to determine whether the stroke volume is determined by the central blood volume This ratio is free from errors in the calibration of the dye dilution apparatus. It may be calculated also as 1/HR MTT and both the heart rate and the mean transit time can be measured more accurately than SV or CBV Therefore it was surprising that there occurred large individual variations in this ratio during hypoxia, although the mean changes in the different groups of lambs were insignificant.

In contrast to lambs, the ratio SV CBV increased by more than 10 per cent ($p < 0.01$) in sheep This difference may be ascribed to improved ventricular function during hypoxia in the sheep which makes an increased stroke volume possible without increased CBV and left ventricular end-diastolic pressure Unfortunately the left atrial pressures were not measured

As presented in the literature review the diving pattern has been found to occur in many mammals in certain circumstances. Elsner *et al.* (40) observed it in calves 10 days after birth. The responses to hypoxia of fetal lambs at term described by Assali *et al.* (8) resemble the diving pattern, for bradycardia, increased carotid and umbilical flows and decreased femoral flow were observed.

The hypoxia experiment on a lamb days old presented in Fig. 11 revealed signs of a diving pattern, i.e. bradycardia and decreased cardiac output. The diving pattern is considered to occur in a seal when it cannot breathe (108) and in a rabbit during hypoxia because its respiratory response to hypoxia is poor (74) The lamb presented here breathed poorly and this caused its arterial pCO_2 to increase above normal. Increased pCO_2 was hardly responsible for the depressed cardiac function, because combined hypoxia and hypercapnia result in increased cardiac outputs (unpublished data)

The development of the diving pattern in newborn mammals remains to be investigated more closely If it is found to occur repeatedly in newborn lambs and infants, it indicates a strong vasomotor control by the central nervous system and would be clinically important

EFFECTS OF HYPERCAPNIA

Hypercapnia is known to increase the cardiac outputs of adult men (6, 8, 10, 104) and dogs (18) The same change was observed in neonatal lambs and 1 month-old sheep in the present study No attempt was made to determine whether the increase in cardiac output of the lambs differed quantitatively from that of the sheep The only clear difference was that increases in both heart rate and stroke volume contributed equally to the increase in cardiac output in lambs whereas a decrease in heart rate occurred during hypercapnia in the sheep The picture of a mature response is supplemented by the observation of Stahlman *et al.* (117) that peripheral vasodilatation occurs during hypercapnia in neonatal lambs.

The mechanism that leads to increased tissue perfusion during hypercapnia seems to

longer than in adult rats (135) Observations on different mammals show that the activities of many enzymes involved in oxidative energy production in the liver increase after birth (30) It would not be surprising if such a change occurs also in the heart The difference in cardiac response to hypoxia between newborn and adult mammals may possibly be due to different enzyme patterns. A comparative study of the enzyme patterns of hearts of newborn and adult mammals would possibly shed some light on the autoregulatory system of the heart.

The most important finding of this study was that the cardiac output of the lambs did not increase during hypoxia when metabolic acidosis prevailed. This was demonstrated by the series of lambs in which increasing degrees of metabolic acidosis were measured (Fig 7) When the B E exceeded —5 meq /l., the cardiac output always increased. At a lower B.E the cardiac output increased at the beginning of the hypoxia experiment and decreased later (Fig 12) At a B E of less than —10 meq /l it remained unchanged or decreased In this last group the cardiac output was low already initially (Fig 6) The reason for this variation of the cardiac output during hypoxia in severe metabolic acidosis may be a lowered oxygen transport to the myocardium It is tempting to think that the initially low output and hypoxia would have caused more rapid progress of metabolic acidosis which in turn would have reduced the cardiac output However the present series did not support this idea because the development of acidosis was similar in all hypoxia groups. The observed decreased cardiac output during hypoxia associated with severe metabolic acidosis agrees with the observation of Downing *et al* (37) that ventricular function is depressed in this condition They also found that hypoxia alone depresses the ventricular function slightly However increased ventricular work is not necessarily required for increased cardiac output during hypoxia if the peripheral resistance decreases sufficiently

There were some age differences between the different groups used in the hypoxia experiments (Table III) The mean ages in groups A B and C were 7.2, 6 0 and 5.1 days, respectively These age differences were not responsible for the differences found in the cardiovascular response to hypoxia because for instance omission of the oldest lamb from group A would have reduced the mean age to that of group B and led to a greater average increase in cardiac output.

The heart rate tended to increase somewhat during hypoxia but the change was not significant. There were large individual variations in the heart rates, and correspondingly the stroke volumes varied greatly in the lambs. The large changes in heart rate possibly indicate variations of the vegetative tone during the experiments. This statement is in agreement with the observations of Harrison *et al* (59) that procedures which change the vegetative balance of the cardiac innervation may alter the heart rate without affecting the cardiac output. The cardiac output is the most important variable controlled by the organism and possible changes in heart rate will be compensated for by changes in stroke volume According to these results, the heart rate cannot be considered an accurate indicator of flow conditions in an individual suffering from hypoxia.

An increased degree of metabolic acidosis did not significantly alter the initial heart rate, and the response to hypoxia was exactly the same a slight increase as in milder acidosis. The variation of the heart rate was greater in mild acidosis than in severe acidosis. These observations on the heart rate in lambs during hypoxia seem to differ from observations on infants suffering from respiratory distress, for infants with the most severe conditions have the highest heart rates (124)

The central blood volume increased in parallel with cardiac output in hypoxia. This

the heart rate. Eight of the nine lambs of this series were anesthetized and hence the heart rate may have been influenced by the drug.

The significant decrease in the ratio SV/CBV in lambs with metabolic acidosis may be due to decreased ventricular performance, i.e. at a given CBV the stroke volume cannot be maintained. This *interpretation* does not agree with the finding of Downing et al. (37) that metabolic acidosis does not significantly decrease the ventricular function of neonatal lambs. Simultaneous measurement of aortic pressure would undountedly have given information about the ventricular function.

The decrease in cardiac output has been explained to be due to lowered glucose uptake by the myocardium (47 49, 95) or to *decreased oxygen supply to the myocardium* resulting from a Bohr shift caused by acidosis. All the experiments of the acidosis series lasted more than two hours, and it is possible that the myocardial glycogen stores were reduced by anaerobic glycolysis. Depletion of myocardial glycogen would depress cardiac function by reducing the immediate glucose supply. Clarification of this aspect awaits *further experiments*.

Metabolic acidosis lowered the central blood volume in most experiments. This observation indicates that blood must have shifted from the lungs to the peripheral vascular beds. This is probably due to a general vasodilatation in metabolic acidosis.

CLINICAL ASPECTS

The conditions which were investigated in the present study are observed in respiratory distress and other clinical conditions accompanied by gas exchange disorders. The sequelae of impaired gas exchange hypoxia and metabolic acidosis also increase pulmonary vascular resistance (105). In acute asphyxia this tendency is opposed by more oxygenated blood which enters the pulmonary circulation from the aorta via the arterial duct (96). *If* hypoxia continues in spite of this, increased pulmonary vascular *resistance* reopening of the arterial duct and decreased aortic pressure lead *to the pulmonary* hypoperfusion (22). This is a condition with impaired gas exchange in the lungs which can be corrected only by a physician, *if at all*.

The present study shows that the oxygen transport is limited in severe metabolic acidosis not only by impaired pulmonary function but also by suppressed cardiac function. Furthermore, the stimulating effect of arterial hypoxia on the heart observed in normal acid-base conditions is not observed in metabolic acidosis. The hypoxic *stimulation of the* cardiac output seems to be depressed already at a B.E. *of —5 meq./l.* The *response* of cardiac output to hypoxia when the B.E. was nearly normal was twofold at best.

The usual treatment for neonatal asphyxia consists of positive pressure insufflation which has been observed to open atelectatic parts of the lungs (96). An increased oxygen partial pressure helps to overcome the effects of decreased pulmonary diffusion. Treatment with alkali-glucose infusion according to Usher (124) has been demonstrated to decrease the pulmonary *vascular resistance (105). The* present study shows that a normal standard bicarbonate level is required to maintain a normal cardiac output. Thus correction of metabolic acidosis improves both cardiac function and pulmonary perfusion. Also hypoxic stimulation of the heart is corrected by reinstitution of a normal standard bicarbonate level.

In contrast to metabolic acidosis, hypercapnia stimulated the cardiac function. This happened also in the lambs with *B.E. of less* than —10 meq./l. A moderately increased level of carbon dioxide may *therefore* be considered advantageous for the circulation during asphyxia, because it is known *to decrease* vascular resistance in peripheral and

be present already in lambs at term The results of Assali *et al* (8) indicate this, because they recorded increased carotid femoral and umbilical arterial flows during hypercapnia. The mechanism leading to in creased cardiac output seems to be dependent on the function of the sympathetic nervous system (92) At least the adrenals of lambs at term are known to respond to asphyxia as well as the adrenals of older sheep (23)

Metabolic acidosis seemed not to depress the cardiac response to hypercapnia. There were two lambs with B E of less than —10 meq /l. and the cardiac output increased to the same extent in these as in lambs with only moderate metabolic acidosis. This result in dicates that an increased level of carbon dioxide in the blood is a more potent stim ulator of the heart than a low oxygen content.

The different responses of the cardiac output in hypercapnia and metabolic acidosis indicate that a decrease in pH does not alone determine the cardiac function in an organism Variations of pCO_2 and standard bicarbonate must therefore have specific effects in all cells or in some receptor cells. The effect of carbon dioxide is the sum of a direct depressant effect on the myocardial function (15) and an increased sympathetic discharge to the heart (92) The influence of the latter is dominant.

The appearance of a total A V block in a lamb with severe metabolic acidosis during hypercapnia shows that the rhythm of the neonatal heart is probably as sensitive to high carbon dioxide pressure as the rhythm of the adult heart (81) No arrhythmias occurred in lambs with only moderate metabolic acidosis. Further studies are required to clarify in detail how metabolic acidosis com bined with hypercapnia affects heart function.

EFFECTS OF METABOLIC ACIDOSIS

The lambs in which metabolic acidosis devel oped were younger than those in which it did not (*Table III*) It seemed to develop more easily in lambs under chloralose anesthesia. The only clearly defined cause of its development was the artificial hypoxia which clearly decreased the standard bicarbonate level (Tables VII and VIII) In many cases, however its origin remained obscure. The lambs which developed metabolic acidosis must have had an anaerobic metabolism which led to increased lactic acid concentrations. No noticeable arterial hypoxia (S_aO less than 90 per cent) was detected in these cases. Thus, the explanation must be something like that given by Graven *et al* (50) the lactic acid concentration of premature infants increases easily during activity and decreases after wards, but less rapidly than in adults. Some lambs with metabolic acidosis, especially those under chloralose anesthesia, breathed rapidly and shivered. The shivering stopped or less ened when the anesthesia was deepened. Rapid distressed breathing continued in many cases in spite of apparently sufficient anesthesia. This may be the physical activity which produced lactic acid If this is true the development of metabolic acidosis indicates that the mechanisms responsible for increased tissue perfusion during physical activity are not mature in neonatal lambs. It is known that physical exercise trains the circulation to effect an appropriate distribution of blood Therefore it is reasonable to assume that newborn animals require some physical activ ity before the circulation can adapt itself to greater demands.

The effect of metabolic acidosis was the same as reported for adult dogs (18 49) The cardiac output decreased by nearly 40 per cent for a decrease of 10 meq l in B.E The arterial pCO decreased at first with B.E but then remained unchanged (Table XI) A low pCO may also have decreased the cardiac output (18)

The variation of the cardiac output was mainly due to a decrease in the stroke volume although there was a slight decrease also in

he heart rate. Eight of the nine lambs of this series were anesthetized and hence the heart rate may have been influenced by the drug.

The significant decrease in the ratio SV/CBV in lambs with metabolic acidosis may be due to decreased ventricular performance, i.e. at a given CBV the stroke volume cannot be maintained. This interpretation does not agree with the finding of Downing *et al.* (37) *that metabolic acidosis does not* significantly decrease the ventricular function of neonatal lambs. Simultaneous measurement of aortic pressure would undoubtedly have given information about the ventricular function.

The decrease in cardiac output has been explained to be due to lowered glucose uptake by the myocardium (47 49, 95) or to decreased oxygen supply to the myocardium *resulting from a Bohr shift caused by acid*osis. All the experiments of the acidosis series lasted more than two hours, and it is possible that the myocardial glycogen stores were reduced by anaerobic glycolysis. Depletion of myocardial glycogen would depress cardiac function by reducing the immediate glucose supply. Clarification of this aspect awaits further experiments.

Metabolic acidosis lowered the central blood volume in *most experiments. This observation* indicates that blood must have shifted from the lungs to the peripheral vascular beds. This *is probably due to* a general vasodilatation in metabolic acidosis.

CLINICAL ASPECTS

The conditions which were investigated in the present stud are observed in respiratory distress and other clinical conditions accompanied by gas exchange disorders. The sequelae of impaired gas exchange hypoxia and metabolic acidosis also increase pulmonary vascular resistance (105). In acute asphyxia this tendency is opposed by more oxygenated blood which enters the pulmonary circulation from the aorta via *the arterial* duct (96). If hypoxia continues in spite of this, increased pulmonary vascular resistance reopening of the arterial duct and decreased aortic pressure lead to the pulmonary hypoperfusion (22). This is a condition with impaired gas exchange in the lungs which can be corrected only by a physician, *if* at all.

The present study shows that the oxygen transport is limited in severe metabolic acidosis not only by impaired pulmonary function *but also by suppressed* cardiac function. Furthermore the stimulating effect of arterial hypoxia on the heart observed in normal acid-base conditions is not observed *in metabolic* acidosis. The hypoxic stimulation of the cardiac output seems to be depressed already at a B.E. of —5 meq./l. The response of *cardiac output to* hypoxia when the B.E. was nearly normal was twofold at best.

The usual treatment for neonatal asphyxia consists of positive pressure insufflation which has been observed to open atelectatic parts of the lungs (96). An increased oxygen partial pressure helps to overcome the effects of *decreased pulmonary diffusion. Treatment* with alkali-glucose infusion according to Usher (104) has been demonstrated to decrease the pulmonary vascular resistance (105). The present study shows that a normal standard bicarbonate level is required to maintain a normal cardiac output. Thus correction of metabolic acidosis *improves both cardiac* function *and pulmonary perfusion.* Also hypoxic stimulation of the heart is corrected by *reinstitution* of a normal standard bicarbonate level.

In contrast to metabolic acidosis, hypercapnia stimulated the cardiac function. This happened also in *the lambs with B.E. of less* than —10 meq./l. A moderately increased level of carbon dioxide may therefore be *considered* advantageous for the circulation during asphyxia, because it is known *to* decrease vascular resistance in peripheral and

pulmonary vascular beds (117) An increased level of carbon dioxide in alveoli improves the pulmonary diffusion capacity for carbon monoxide in man (100)

The opposite effects of hypercapnia and metabolic acidosis on the heart suggest that a decreased pH alone is not disadvantageous. A decrease in the standard bicarbonate level obviously must be corrected in a distressed infant A moderate increase in the carbon dioxide level does not seem to require corrective measures if it is not a sign of reduced oxygen exchange in the lungs.

Signs of the diving pattern were observed in one lamb during hypoxia This pattern probably develops also in human infants (65, 108) Apparently this kind of circulatory adjustment occurs in pale infants or infants with cyanotic hands and feet If it involves large parts of the circulation the condition should probably be treated according to the principles of shock therapy This includes administration of drugs that promote peripheral vasodilatation in constricted parts of the circulation and cardiac function and measures that effect sufficient oxygenation

Summary

The aim of the present study was to investigate the cardiovascular responses of neonatal lambs to acute hypoxia, hypercapnia and metabolic acidosis for a clarification of the significance of these states in neonatal asphyxia. Basal circulatory values were measured using the dye dilution method. Another aspect studied was the effect of chloralose on the cardiovascular function of neonatal lambs.

The average basal cardiac output underwent an almost significant increase from 200 to 300 ml/min/kg between the ages of 36 hours and 8 days and decreased subsequently to 60 ml/min/kg in sheep 1[illegible] months old. The mean heart rate which was 185 per minute in unanesthetized lambs less than 30 days old, was 140 per minute in the sheep. During this period from one to twelve months the stroke volume decreased from 1.45 to 0.60 ml/kg. CBV changed in parallel with the cardiac output. It increased from 16 to 23 ml/kg between the ages of 36 hours and 8 days and decreased to 1[illegible] ml/kg in sheep 1[illegible] months old. The appearance time increased linearly from [illegible] to [illegible].9 seconds during the same period. Evidence was found that AT is directly proportional to the ratio of CBV to cardiac output.

Chloralose was found to increase the mean heart rate of lambs less than 30 days old from 185 to [illegible]40 per minute. Concurrently the stroke volume and ratio SV/CBV decreased. The anesthetic did not have any effect on the cardiac output, central blood volume or appearance time.

During acute arterial hypoxia (S_aO_2 67 per cent on average) induced with 10 per cent oxygen in nitrogen, the mean cardiac output of the lambs increased by 31 to 35 per cent when the acid-base conditions were normal. When moderate metabolic acidosis was present (B.E. —5 to —10 meq./l.) the mean cardiac output did not rise significantly during hypoxia. If an increase occurred in an individual lamb, a return to the normal output or a lower output occurred within 10 minutes. In severe metabolic acidosis (B.E. less than —10 meq./l.) the cardiac output decreased during hypoxia almost significantly. This change was due to a decreased stroke volume.

The heart rates of the lambs increased insignificantly during acute hypoxia; the degree of metabolic acidosis did not influence this response. The reliability of heart rate as an indicator of flow conditions during hypoxia is discussed. Central blood volume varied in parallel with cardiac output during hypoxia.

The response of sheep over 6 months old to hypoxia was clearly stronger than that of neonatal lambs with a normal acid-base balance. When the mean arterial oxygen saturation was 67 per cent, the cardiac output increased by 65 per cent in the sheep. This was due to an increase in the stroke volume.

Acute hypercapnia (pCO_2 76 mmHg on average) caused the cardiac outputs of lambs to increase by 97 per cent on average. Increases of both stroke volume and heart rate contributed equally to this change. Metabolic acidosis did not seem to depress the cardiac response to hypercapnia, because also lambs with B.E. less than —10 meq./l. showed increased cardiac outputs. Central blood volume increased during hypercapnia. Chloralose influenced the cardiac response to hypercapnia

almost significantly by suppressing the increases in both cardiac output and heart rate. The cardiovascular changes resulting from hypercapnia in sheep 12 months old differed from those in neonatal lambs in that the heart rates decreased in the sheep but increased in the lambs.

Metabolic acidosis developed during the hypoxia experiments and also spontaneously in the lambs. The mechanism of its spontaneous development is discussed. A decrease of 10 meq./l. in B.E. lowered the cardiac output by almost 40 per cent. This was mainly due to a decrease in the stroke volume.

The clinical application of the knowledge gained in this study is discussed. The results indicate that prevention or correction of metabolic acidosis improves the cardiac function in addition to improving the pulmonary perfusion as observed by other workers. Both of these effects increase the transport of oxygen from the lungs to the tissues. Moderate hypercapnia may even be favorable from the standpoint of cardiovascular function.

Acknowledgements

The present investigation was carried out at the Cardiorespiratory Research Unit and the Department of Physiology University of Turku, in 1965—67 My thanks are due to the staffs of these institutions for their co-operation and support during the study

I am deeply grateful to my chief, Professor Tuomas Peltonen, M.D Head of the Children s Hospital, University of Turku, and to Associate Professor Leo Hirvonen, M.D Head of the Cardiorespiratory Unit. *They have investigated fetal and neonatal* cardiorespiratory phenomena for over ten years and created the present facilities for studies in this field in Turku. Their support has been of great value.

My thanks are due also to Professor Kaarlo Hartiala, M D Head of the Department of Physiology of which the Cardiorespiratory Unit is a section, for his interest in my work.

I also wish to express my thanks to Mr Erkki Soini, Ph.M., for his help and advice in the construction of the dye dilution equipment and to the medical students who assisted me during the experiments.

I am grateful to Mrs. Seija Kesäniemi, Ph.M., for the statistical analyses, to Mrs. Liisa Karkola, M.A., for help in collecting the literature, and to Miss H Aaltonen for help in the preparation of the manuscript.

I am indebted to Mr E R. Korte Ph.M., for his revision of the manuscript.

Lääke OY medicinal factory Turku, commissioned its art department to draw the *figures of this publication. I wish to thank* the directors of the company and the artists for this assistance.

A research stipend received from the Lastentautien Tutkimussäätiö in the early stages of this study is gratefully acknowledged. Grants awarded by the Sigrid Jusélius and the Yrjö Jahnsson Foundations to the Cardiorespiratory Research Unit have also supported my work, for which I am grateful

Turku, April, 1969

Antti Koivikko

almost significantly by suppressing the increases in both cardiac output and heart rate. The cardiovascular changes resulting from hypercapnia in sheep 12 months old differed from those in neonatal lambs in that the heart rates decreased in the sheep but increased in the lambs.

Metabolic acidosis developed during the hypoxia experiments and also spontaneously in the lambs. The mechanism of its spontaneous development is discussed. A decrease of 10 meq./l. in B.B. lowered the cardiac output by almost 40 per cent. This was mainly due to a decrease in the stroke volume.

The clinical application of the knowledge gained in this study is discussed. The results indicate that prevention or correction of metabolic acidosis improves the cardiac function in addition to improving the pulmonary perfusion as observed by other workers. Both of these effects increase the transport of oxygen from the lungs to the tissues. Moderate hypercapnia may even be favorable from the standpoint of cardiovascular function.

23. Comline, R. S. and Silver, M. Development of activity in the adrenal medulla of the foetus and new-born animal. Brit. med. Bull. 22 16, 1966.

24. Cooper, K. E., Greenfield, A. D. M. and Huggett, A. St G. The umbilical blood flow in the foetal sheep. J. Physiol. (Lond.) 108 160, 1949

25. Cross, K. W., Tizard, J. P. M. and Trythall, D. A. H. The gaseous metabolism of the new born infant breathing 15% oxygen. Acta paediat. scand. 47 217 1958.

26. Cross, K. W., Dawes, G. S. and Mott, J. C. Anoxia, oxygen consumption and cardiac output in new born lambs and adult sheep. J. Physiol. (Lond.) 146 316, 1959

27. Darby, T. D., Aldinger, E. E., Gadsden, R. H. and Thrower, W. B. Effects of metabolic acidosis on ventricular isometric systolic tension and the response to epinephrine and levarterenol. Circulat. Res. 8 1242, 1960.

28. Dawes, G. S., Mott, J. C. and Widdicombe, J. G. The foetal circulation in the lamb. J. Physiol. (Lond.) 126 563, 1954.

29. Dawes, G. S. Changes in the circulation at birth. Brit. med. Bull. 17 148, 1961.

30. Dawkins, M. J. R. Biochemical aspects of developing function in new-born mammalian liver. Brit. med. Bull. 22 27 1966.

31. Ditchburn, R. K., Hull, D. and Segall, M. M. Oxygen uptake during and after positive-pressure ventilation for the resuscitation of asphyxiated newborn infants. Lancet 2 1096, 1966

32. Donald, D. E., Ferguson, D. A. and Milburn, S. E. Effect of beta-adrenergic receptor blockade on racing performance of greyhounds with normal and with denervated hearts. Circulat. Res. 22 127 1968.

33. Downing, S. E., Remensnyder, J. P. and Mitchell, J. H. Cardiovascular responses to hypoxic stimulation of the carotid bodies. Circulat. Res. 10 676, 1962.

34. Downing, S. E., Mitchell, J. H. and Wallace, A. G. Cardiovascular responses to ischemia, hypoxia and hypercapnia of the central nervous system. Amer. J. Physiol. 204 881 1963.

35. Downing, S. E., Talner, N. S. and Gardner, T. H. Cardiovascular responses to metabolic acidosis. Amer. J. Physiol. 208 237 1965.

36. Downing, S. E., Talner, N. S. and Gardner, T. H. Influences of hypoxemia and acidemia on left ventricular function. Amer. J. Physiol. 210 1327 1966.

37. Downing, S. E., Talner, N. S. and Gardner, T. H. Influences of arterial oxygen tension and pH on cardiac function in the newborn lamb. Amer. J. Physiol. 211 1203, 1966.

38. Doyle, J. T., Wilson, J. S. and Warren, J. V. The pulmonary vascular responses to short-term hypoxia in human subjects. Circulation 5 263, 1952.

39. Elliott, K. A. C. and Wolfe, L. S. Brain tissue respiration and glycolysis. Neurochemistry. The chemistry of brain and nerve. 2. ed. Ed. by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield, Ill. 1962. Thomas.

40. Elsner, R., Franklin, D. L., van Citters, R. L. and Kenney, D. W. Cardiovascular defense against asphyxia. Science 153 941, 1966.

41. Fishman, A. P., Fritts, H. W. Jr. and Cournand, A. Effects of acute hypoxia and exercise on the pulmonary circulation. Circulation 22 204, 1960.

42. Fishman, A. P., Fritts, H. W. Jr. and Cournand, A. Effects of breathing carbon dioxide upon the pulmonary circulation. Circulation 22 220 1960.

43. Fritts, H. W. Jr., Braunwald, E., Fishman, A. P. and Cournand, A. Influence of induced hypoxia on central blood volume of normal man. Fed. Proc. 13 68, 1954.

44. Fritts, H. W. Jr., Harris, P., Clauss, R. H., Odell, J. E. and Cournand, A. The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. J. clin. Invest. 37 99 1958.

45. Fritts, H. W. Jr., Odell, J. E., Harris, P., Braunwald, E. W. and Fishman, A. P. Effects of acute hypoxia on the volume of blood in the thorax. Circulation 22 216, 1960.

46. Gasul, B. M., Marino, J. J. and Christian, J. R. Fluorescein circulation time in normal and pathologic conditions in infants and children, including various types of congenital malformations of the heart. J. Pediat. 34 460, 1949.

47. Gercken, G. Glucose-, Milchsäure-, ATP- und ADP-Konzentration in Arteriolen und venösem Coronarblut des Hundes bei Sauerstoffmangel. Pflügers Arch. ges. Physiol. 272 322, 1961.

48. Gömöri, P., Kovách, A. G. B., Takács, L., Földi, M., Szabó, Gy., Nagy, Z., Wiltner, W. and Kállay, K. The regulation of cardiac output in hypoxia. Acta med. Acad. Sci. hung. 16 93, 1960.

49. Goodyer, A. V. N., Eckhardt, W. F., Ostberg, R. H. and Goodkind, M. J. Effects of metabolic acidosis and alkalosis on coronary blood flow

References

1 ACHESON G H DAWES, G S. and MOTT J C. Oxygen consumption a d the arterial oxygen saturation in foetal and new born lambs. J Physiol. (Lond.) 135: 623, 1957

– ADAMSONS, K JR., BEHRMAN R., DAWES, G S., DAWKINS, M J R., JAMES, L. S. and ROSS B. B: The treatment of acidosis with alkali and glucose during asphyxia in foetal Rhesus mon keys. J Physiol. (Lo d.) 169 679 1963.

3. ALBERS, C. and USINGER, W Der Kreislauf des Hundes bei akutem Sauerstoffmangel. Pflügers Arch. ges. Physiol. 263 201, 1956.

4. ARCILLA, R. A., OH, W WALLGREN G HANSON J S., GESSNER, I. H. and LIND J Quantitative studies of the human neonatal circulation. II Hemodynamic findings in early and late clamping of th umbilical cord. Acta paediat. scand., S ppl. 179: 23, 1967

5. ARDRAN G M DAWES, G. S., PRICHARD M. M L., REYNOLDS, S. R. M and WYATT D G: The effect of ventilation of the foetal lungs upon the pulmonary circulation. J Physiol. (Lond.) 118: 12, 1952.

6. ASMUSSEN E. CO_2-breathing and output of the heart. Acta physiol. scand. 6 176 1943.

ASSALI N S., RAURAMO, L. and PELTONEN T Measurement of uterine blood flow and uterine metabolism. VIII. Uterine and fetal blood flow and o ygen consumption in early human preg nancy Amer J Obstet. Gynec. 9 86, 1960.

8. ASSALI N S., HOLM L. W and SEHGAL, N Hemodynami changes in f tal lamb in utero in response to asphyxia, hypoxia and hypercapnia. Circulat. Res. 11 423, 196–

9 ASSALI N S., MORRIS, J A. and BECK, R. Cardiovascular hemodynamics in the f t l lamb before a d after lung expansion. Amer J Physiol. 208: 122, 1965.

10 AULD, P A. M DAVENPORT H T SEKELJ P JEGIER, W BEAUDRY P and MCGREGOR, M The ffect of increased pCO_2 o cardiac output during respiratory control in th anesthetized hild. Canad. med. Ass. J 86 212, 1962.

11. AVIADO D M. JR., CERLETTI A., ALANIS, J BULLE, P H and SCHMIDT C F Effects of anoxia on pressure resistance and blood (P^{32}) volume of pulmonary vessels. Amer J Physiol. 169: 460 195–

12. BARCROFT J a d TORRENS, D S. The output of the heart of the foetal sheep. J Physiol (Lond.) 105: 22 P 1946—1947

13. BIERMAN H R. Pulmonary circulation times with particular relationship to acute hypoxia. Amer J med. Sci. 221: 16–, 1951

14. BLANKENSHIP W LIND, J and ARCILLA, R. A. Atrial pressures and pulmonary circulation time in the newborn inf nt Acta paediat. scand. 54: 446, 1965.

15. BONIFACE, K. J and BROWN J M: Effect of carbon dioxide excess on contractile force of heart in situ. Amer J Physiol. 172: 52, 1953.

16. BRADY J P and CERUTI E. Chemoreceptor reflexes in the new born infant effects of varying degrees of hypoxia on heart rate and ventilation in a warm environment. J Physiol. (Lond.) 184 631 1966.

17 BROWN E. B. JR. and MILLER, F: Ventricular fibrillation following a rapid fall in al eolar carbon dioxide concentration. Amer J Physiol. 169 56, 195–

18. CARSON S. A. A CHORLEY G E., HAMILTON F N LEE, D C and MORRIS, L. E.: Variation in cardiac output with acid-base changes in the anesthetized dog J appl. Physiol. 20 948, 1965.

19 CELANDER, O and MÅRILD, K. Reactive hyperaemia in the foot and calf f the newborn infant Act paediat scand. 51 544, 196–

20. CELANDER, O St dies of the peripheral circu lation. In The heart and circulation in the newborn and infant Ed. by D E. Cassels. New York & Londo 1966. Grune & Stratton

21 CHIDSEY C. A., FRYE, R. L., KAHLER, R. L. and BRAUNWALD, E: Influence of syrosingopine o the ca diovascular response t acut hypo emia nd e ercise Circulat. Res. 9 989 1961

22. CHU J CLEMENTS, J A., COTTON E., KLAUS, M. H SWEET A. Y THOMAS, M A. and TOOLEY W H The pulmonary hypoperfusi n yndrome Pr liminary report Pediatrics 35 733 1965.

T Circulation times in newborn infants by the fluorescein method. Amer J Dis. Child. 83 643, 1952.

78. Lilienfeld, L and Dinckerter, G Comparison of the Fick and dye injection methods for measuring the cardiac output in acute hypoxia. Exp. Med. Surg. 11 258, 1953.

79. Levinson, H., Delivoria Papadopoulos, Maria and Swyer, P R. Oxygen consumption in newly born infants with the respiratory distress syndrome. Biol. Neonat. (Basel) 7 255, 1964.

80. Lubliny G. von Die Wirkung der Chloralose auf das Elektrokardiogramm. Zur Pharmakologie der Chloralose. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. 167 717 1932.

81. MacDonald, P M. and Simonson, E. Human electrocardiogram during and after inhalation of thirty per cent carbon dioxide. J ppl. Physiol. 6 304, 1953—1954.

82. McGregor, M., Donevan, R. E. and Anderson, N. M. Influence of carbon dioxide and hyperventilation on cardiac output in man J ppl. Physiol. 17 933, 1962.

83. McGuire, J Westcott R. N and Fowler, N. O. Anoxia and human pulmonary vascular resistance Trans. Ass. Amer Physns. 64 404, 1951.

84. Mahon W A., Goodwin J W and P ul, W M. Measurement of individual ventricular outputs in the fetal lamb by a dye dilution technique. Circulat. Res. 19 191, 1966.

85. Marshall, R. J and Shepherd, J T Interpretation of changes in "central" blood volume and slope volume during exercise in man J clin. Invest. 40 375, 1961.

86. Meier, P and Zierler, K. L. On the theory f the indicator dilution method for measurement of blood flow and volume J appl. Physiol. 6 731, 1953—1954.

Méndez B ... C Poseiro, J J Arellano-Hernández, G., Zambrana, M. A. and Caldeyro-Barcia, R. Effects of atropine on the heart rate f the human fetus during labor Amer J Obstet Gynec. 85 1033, 1963.

Nahas, G. G. Visscher, M. B. and Haddy F J Discrepancies in cardiac output measurements by t pplications f the direct Fick principle J ppl. Physiol. 6 292, 1953—1954.

89. Nahas, G. G., Visscher, M. B., Mather, G. W Haddy F J and Warner, H. R. I fluence f hypoxia on the pulmonary circulation f nonnarcotized dogs. J ppl. Physiol. 6 467 1953—1954.

90. Nahas, G. G., Mather, G. W Wargo, J D. M. and Adams, W L. Influence of acute hypoxia on sympathectomized and adrenalectomized dogs. Amer J Physiol. 177 13, 1954.

91. Nahas, G G. and L'Allemand, H. Circulation in dogs aft respiratory arrest induced by curare J ppl. Physiol. 8 408, 1956.

92. Nahas, G. G. and Cavert H. M. Cardiac depressant effect f CO, and its reversal. Amer J Physiol. 190 483, 1957

93. Oberst B. B. and LaRocke, F Circulation time in the newborn infant, using the fluorescein dy method. J Pediat. 44 536, 1954.

94. Oliver, T K. Jr. and Karlberg, P The ffects of environmental temperature and 15 % oxygen in the inspired air on the gaseous metabolism of newly born human infants. Amer J Dis. Child. 104 348, 1962.

95. Opie, L. H., Kadas, T and Gevers, W Effect of pH on the function and glucose metabolism of the heart. Lancet 2 551, 1963.

96. Peltonen, T and Hirvonen L. Experimental studies on fetal and neonatal circulation. Acta paediat. scand., Suppl. 161, 1965.

97 Penna, M., Soma, L. and Aviado, D M. Role of carotid and aortic bodies in mediating the increase in cardiac output during anoxemia. Amer J Physiol. 203 133, 1962.

98. Prec K. J and Cassels, D E. Dye dilution curves and cardiac output in newborn infants. Circulation 11 789 1955.

99. Price, H. L. Effects f carbon dioxide on the cardiovascular system. Anesthesiology 21 652, 1960.

100. Rankin J McNeill, R. S. and Forster, R. E. Influence f increased alveolar carbon dioxide tension on pulmonary diffusing capacity for CO in man. J ppl. Physiol. 15 543, 1960.

101. Reeves, J T and Leathers, J E. Circulatory changes following birth of the calf and the ffect f hypoxia. Circulat. Res. 15 343, 1964.

102. Richardson D. W Wasserman A. J and Patterson, J L. Jr. General and regional circulatory responses to change in blood pH and carbon dioxide tension. J Clin. Invest. 40 31, 1961.

103. Richardson D. W Kontos, H. A., Raper, A. J and Patterson, J L. J Modification by beta-adrenergic blockade of the circulatory responses to acute hypoxia in man. J clin. Invest. 46 77 1967

104. Rosenberg, R. The effect of altered blood carbon dioxide tension and pH on the human pulmonary circulation. Scand. J clin. Lab. Invest. 18 Suppl. 90, 1966.

105. Rudolph, A. M. and Yuan S. Response of the pulmonary vasculature to hypoxia and H

and myocardial metabolism in the intact dog Amer J Physiol. 200 628, 1961

50 GRAVEN S. N CHISCUOLO, D and HOLCOMB T M. The effect of activity on the conce tration of blood lactate in newborn infants. Pediatrics 37 278, 1966

51 GREEN H. D and KEPCHAR, J H. Control of peripheral resistance in major systemic vascular beds. Physiol. Rev 39: 617 1959

52. GRIBBE, P HIRVONEN L. and PELTONEN T Lung circulation at different ages. Acta physiol. scand. 50 Suppl. 175 61 1960

53. GROLLMANN A.: Physiological variations of the cardiac output of man: VII. Effect of high altitude on cardiac output and its related functions and account of experiments conducted on the summit of Pike s Peak, Colorado. Amer J Physiol. 93 19 1930

54. GUYTON A. C. Circulatory physiology Cardiac output and its regulation. Philadelphia and London 1963. Saunders.

55. HAKULINEN A., HIRVONEN L. and PELTONEN T: Response of blood pressure to sucking and tilting in the newborn infant. Ann. Paediat. Fenn. 8 58, 1962.

56. HAMILTON W F MOORE, J W KINSMAN J M. and SPURLING R. G: Studies on the circulation IV Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Amer J Physiol. 99: 534, 1932.

57 HÄNNINEN A., PELTONEN T and HIRVONEN L. Response of blood pressure to sucking and tilting in the newborn premature infant. Ann. Paediat. Fenn. 10 92, 1964.

58. HARRISON T R. and BLALOCK, A. The regulation f circulation. VI The effects of severe anoxemia of short duration on the cardia out put of m rphinized dogs and trained unnar cotized dogs. Amer J Physiol. 80: 169 1927

59 HARRISON T R., BLALOCK, A., PILCHER, C. and WILSON C. P The regulation of circulation. VIII. The relative importance of nervous, endocrine and vascular regulation in the response of th cardiac o tput to anoxemia. Am J Physiol. 83 284 1927

60 HEGGLIN R., RUTISHAUSER, W und KAUFMANN G LÜTHY E., SCHEU H Kreislaufdiagnostik mit der Fa bstoffverdünnungsmethode. Stuttgart 1962. Thieme.

61. HOCHREIN M. and KELLER, C J Wechselbeziehungen der Blutdepots. Klin. Wschr 11: 1374 1932.

62. ISSELHARD W: Metabolism and function of the heart during acute asphyxia and in postasphyxial recovery Acta anaesth. scand., Suppl. 9 203, 1968.

63. JALAVISTO, E., MERTENS, O and SCHOEDEL, W: Zur Steuerung der Muskeldurchblutung nach hytmischer Tätigkeit Pflügers Arch. ges. Physiol. 249 167 1948.

64. JAMES, L. S. and ROWE, R. D The pattern of response of pulmonary and systemic arterial pressures in newborn and older infants to short periods of hypoxia. J Pediat. 51 5, 1957

65. JAMES, L. S Acidosis of the newborn and its relation to birth asphyxia. Acta paediat. scand. 49 Suppl. 122 1 1960

66. JEGIER, W BLANKENSHIP W LIND J and KITCHIN A. The changing circulatory pattern of the newborn infant stu lied by the indicator dilution technique. Acta paediat scand. 53: 541 1964.

67 JENKINS, M. T JONES, R. F WILSON B. and MOYER, C. A. Congestive atelectasis a compli cation f the intra e ous infusion of fluids. Ann. Surg 132: 327 1950.

68. JOHNSON S. R.: The effect f some anaesthetic agents on the circulation in man. Acta chir scand., Suppl. 158 1 1951.

69 KARLBERG, P MOORE, R. E., and OLIVER, T K. JR.: Thermogenic and cardiovascular responses of the newborn baby to noradrenaline. Acta paediat. scand. 54 225, 1965

0. KILBURN K. H.: Movement of potassium during acute respiratory acidosis and recovery J appl. Physiol. 21 679 1966.

71 KOCH, G and WENDEL, H. Adjustment of arterial blood gases and cid base balance in the normal newborn infant during the first week of life. Biol. Neonat. (Basel) 12 136, 1968.

72. KOIVIKKO, A: Studies on the haemodynamics of the lamb in the newborn period Act physiol. scand. 68 Suppl. 277 110 1966.

73. KORNER, P I. Circulatory adaptations in hypoxia. Physiol. Rev 39 687 1959

74. KORNER, P I Co trol of the systemic circulation in hypoxia. Proc. Intern. Union Physiol. Sci. 4 137 1963.

75. KRISTOFFERSEN M B., RATTENBORG C. C. and HOLADAY D A. Asphyxial death the roles of acute anoxia, hypercarbia and cidosis. Anesthesiology 28 488, 1967

76 KU DA, H BROWN A. M., THORNE, J L., LANGE, R. L. and HECHT H. H Pulmonary ascular response to acute h poxia in normal, unanesthetized cal es. Ame J Physiol. 203 391 1962.

77 LESAGE, R. E., MEYER, R. and HENDERSON A

T Circulation times in newborn infants by the fluorescein method. Amer J Dis. Child. 83 643, 1952.

78. Lauer L and Deneghetti, G. Comparison of the Fick and dye injection methods for measuring the cardiac output in acut hypoxia. Exp. Med. Surg. 11 258, 1953.

79. Levison H., Delivoria Papadopoulos, Maria and Swyer, P R. Oxygen consumption in newly born infants with the respiratory distress syndrome. Biol. Neonat. (Basel) 7 255, 1964.

80. Lubany G. von Die Wirkung de Chloralose auf das Elektrokardiogramm. Zur Pharmakologie der Chloralose. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. 167 717 1932.

81. MacDonald, F A. and Simonson, E. Human electrocardiogram during and after inhalation of thirty per cent carbon dioxide. J appl. Physiol. 6 304, 1953—1954.

82. McGregor, M., Donevan, R. E. nd Anderson, N. M. Influence of carbon dioxide and hyperventilation on cardiac output in man. J ppl. Physiol. 17 933, 1962.

83. McGuire, J Westcott R. N. and Fowler, N O. Anoxia and human pulmonary ascular resistance. Trans. Ass. Amer Physns. 64 404, 1951.

84 Mahon W A Goodwin J W and P ul, W M. Measurement f individual ventricular outputs in the fetal lamb by dy dilution technique. Circulat. Res. 19 191 1966.

85. Marshall, R. J and Shepherd, J T Interpretation of hanges in central" blood volume and slope slume during exercise in man. J clin. Invest. 40 375, 1961.

86 Meier, P and Zierler, K. L On the theory of the indicator-dilution method for measurement f blood flow and olume J ppl. Physiol. 6 731, 1953—1954

87 Méndez Bauer, C., Poseiro, J J Arellano-Hernández, G., Zambrana, M. A. and Caldeyro-Barcia, R. Effects f atropine on the heart rate f the human fetus during labor Amer J Obstet Gynec 85 1033, 1963.

88 Nahas, G. G Visscher, M. B. and Haddy F J Discrepancies in cardiac output measurements by t pplications of the direct Fick principle. J ppl. Physiol. 6 292, 1953—1954.

89 Nahas, G. G Visscher, M. B., Mather, G. W Haddy F J and Warner, H. R. Influence of h poxia on the pulmonary circulation f nonnarcotized dogs. J appl. Physiol. 6 467 1953—1954.

90 Nahas, G. G., Mather, G. W Wargo, J D M. and Adams, W L. Influence f acute hypoxia on sympathectomized and adrenalectomized dogs. Amer J Physiol. 177 13, 1954.

91. Nahas, G. G. and Ligou, Allemann, H. Circulation in dogs after respiratory arrest induced by curare J ppl. Physiol. 5 405, 1953.

92. Nahas, G. G. and Cavert H. M. Cardiac depressant ffect of CO, and its reversal. Amer J Physiol. 190 483, 1957

93. Oberst B. B. and LaRoche, F Circulation time in the newborn infant, using the fluorescein dy method. J Pediat. 44 560, 1954.

94. Oliver, T K. Jr. and Karlberg P The effects f en ironmental temperature and 15 % oxygen in the inspired air on the gaseous metabolism of newly born human infants. Amer J Dis. Child. 104 348, 1962.

95. Opie, L. H., Kadas, T and Gevers, W Effect of pH on the functio and glucose metabolism of the heart. Lancet 2 551, 1963.

96. Peltonen T and Hirvonen L. Experimental studies on fetal and neonatal circulation. Acta paediat. scand., Suppl. 161, 1965.

97 Penna, M., Soma, L. and A iado, D. M. Role f carotid and aortic bodies in mediating the increase in cardiac output during anoxemia. Amer J Physiol. 203 133, 1962.

98. Prec, K. J and Cassels, D E. Dy dilution curves and cardiac output in newborn infants. Circulation 11 789 1955.

99 Price, H. L. Effects of carbon dioxide on the cardiovascular system. Anesthesiology 21 652, 1960.

100. Rankin J McNeill, R. S. and Forster, R. E. I fluence f increased alveolar carbon dioxide tension on pulmonary diffusing capacity for CO in man. J ppl. Physiol. 15 543, 1960.

101. Reeves, J. T and Leathers, J. E. Circulatory changes following birth of the calf and the effect of hypoxia. Circulat. Res. 15 343, 1964.

102. Richardson D. W Wasserman A. J and P tterson J. L. Jr. General and regional circulatory responses to change in blood pH and carbon dioxide tension. J clin. In est. 40 31, 1961.

103. Richardson D. W Kontos, H. A., Raper, A. J and P tterson J. L. Jr. Modification by beta adrenergic blockade f the circulatory responses to acute hypoxia in man. J clin. Invest. 46 77 1967

104. Rokseth, R. The effect of altered blood carbon dioxide tension and pH on the human pulmonary circulation. Scand. J clin. Lab. Invest. 18 Suppl. 90, 1966.

105. Rudolph, A. M. and Yuan, S. Response of the pulmonary vasculature t hypoxia and H

ion concentration changes. J clin. Invest. *45* 399 1966.

106. RUSHMER, R. F Cardiovascular dynamics. — ed. Philadelphia and London 1961 Saunders.

107 SACKNER, M. A., WILL, D. H and DUBOIS, A. B. The site of pulmonary vasomotor activity during hypoxia or serotonin administration. J clin. Invest. *45* 112, 1966.

108. SCHOLANDER, P F Animals in aquatic environments: diving mammals and birds. In: Handbook of Physiology 4: Adaptation to the environment. Washington 1964. American Physiological Society

109 SCOPES, J W: Metabolic rate and temperature co trol in the human baby Brit. med. Bull. *22*: 88, 1966.

110. SECHZER, P H., EGBERT L. D LINDE, H. W COOPER, D Y DRIPPS, R. D and PRICE, H. L.: Effect of CO_2 inhalation on arterial pressure ECG and plasma catecholamines nd 17-OH corticosteroids in normal man. J ppl. Physiol. *15* 454, 1960

111 SECKEL, H. Die normale Blutumlaufsdauer und Kreislaufgrösse in den ersten beiden Lebensjahren. Kinderheilk. *151* 87 1931.

112. SHABETAI R., FOWLER, N O and HURLBURT O Hemodynamic studies of dogs under pentobarbital and morphine chloralose anesthesia. J surg Res. *3*: 263 1963.

113. SIGGAARD ANDERSEN O., ENGEL, K., JØRGENSEN K. and ASTRUP P A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. Scand. J clin. Lab. In est. *12*: 17., 1960.

114. SIGGAARD ANDERSEN O. and ENGEL, K.: A new acid base nomogram. An improved method fo the calculation of the relevant blood acid base data. Scand. J clin. Lab. Invest. *12*: 177 1960.

115. SJÖSTRAND T The significance of the pulm nary blood volume in the regulation f the blood circulation under normal and patholog ical co ditions. A ta med. scand. *145* 155 19.3.

116. SLOBODY L. B., ROOK G D LEVBARG, M. and MORCY M. Studies of the cardi ascula and renal sy tems in the newly born infant using fluorescein. I Circulation time immediat ly after birth. Pediatrics *6*: 234, 1950

117 STAHLMAN M GRAY J YOUNG W C. and SHEPARD, F M. Cardiovascula response of the neonatal lamb to hypoxia and hyperenpnia. Amer J Physiol. *213* 899 1967

118. STORSTEIN O. The effect f pure xygen breathing on the circulation in anoxemia. Acta med. scand. *143*: Suppl. 269 195..

119. STROUD R. C. and RAHN H: Effects of O_2 and CO_2 tensions upon the resistance of pulmonary blood vessels. Amer J Physiol. *172*: 211, 1953.

120 STROUD, R. C. and CONN H L. JR.: Pulmonary vascular effects of moderate and severe hypoxia in the dog Amer J Physiol. *179* 119 1954

1 1 SUUTARINEN T: Cardiovascular response to changes in arterial carbon dioxide tension. An experimental study on thoracotomized dogs. Acta physiol. scand. *67*: Suppl. 266, 1966.

122. THILENIUS, O. G HOFFER, P B. and FITZ GERALD R. S.: Response of the pulmonary ascular bed of unanesthetized resting dogs to hypoxia. Fed. Proc. *20*: 104 1961.

123. THORP R. H. and COBBIN L. B.: Cardiac stimulant substances. New York and London. Academic Press.

1 4. USHER, R. The respiratory distress syndrome of prematurity Clinical and therapeutic aspects. Pediat Clin. N Amer *8* 5..3, 1961

1..5. USHER, R. Reduction of mortality from respir atory distress syndrome of prematurity ith early administration f intravenous glucose and sodium bicarbonate Pediatrics *32*: 966, 1963.

126. USHER, R., SHEPHARD M. and LIND, J The blood olume of the newborn inf t and placental transfusion. Acta paediat scand. *52*: 497 1963.

1 7 WALLGREN G HANSON J S. and LIND, J: Quantitative studies of the human neonatal circulation. III Observations on the newborn infant central circulatory responses to moderate hypovolemia. A ta paediat. scand., Suppl. 179: 43 1967

128. WALLGREN G HANSON J S., TABAKIN B. S, RAIHA N nd VAPAAVUORI E. Quantit tiv studies f the human neonatal circulation. V Hemodynamic findings i premature infants with d without respiratory distress. A ta paediat sca d., Suppl. 179: 69 1967

129 WANG C S. C., LEVISON H MUIRHEAD D M BOSTON R. W and SMITH C A. Relationship f blood la tat t acidosis d hypoxia in respirat ry distress yndrome J Pediat. *63* 732, 1963

130 WARNER, H R., SWAN J H C., CON OLLY D. C., TOMPKINS, R. G and WOOD, E. H Quantita tio of beat to-beat changes in stroke olume from the ortic pulse contou in man. J appl. Physi l. *5* 495, 1952—1953.

131 WENDLING M G ECKSTEIN J W and ABBOUD, F M: Cardiovascula responses t carbon dioxide bef re and ft beta-adrenergic blockade J ppl. Physiol. *22* 223, 1967

13.. WESTCOTT R. N FOWLER, N O SCOTT R. C., HAUENSTEIN V D and McGUIRE, J: Anoxia

and human pulmonary vascular resistance. J clin. Invest. 40 937 1961.

133. Wiggers, H. C. Cardiac output and total peripheral resistance measurements in experimental dogs. Amer J Physiol. *140* 519, 1943—1944.

134. Visscher, M. B. and Johnson, J. A. The Fick principle analysis of potential errors in its conventional application. J Appl. Physiol. *5* 635, 1952—1953.

135. Wittels, B., Sidbury J. B. Jr. and Huang, S. Y. Influence of age and pulmonary pathology on myocardial glycogen concentration and phosphorylase activity Amer J Dis. Child. *104* 307 1962.

136. Wittenborg, C. M. and Coffey H. G. Circulation time in infants and young children determined by the fluorescein method. J Pediat. *22* 726, 1943.

137. Woods, E. F and Richardson J. A. A survey of agents producing cardiovascular manifestations of epinephrine discharge J Pharmacol. exp. Ther *114* 445, 1955.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 190 1969

EXPERIMENTAL STUDIES ON CLOSURE OF THE DUCTUS ARTERIOSUS UTILIZING WHOLE-BODY FREEZING

BY P YNGVE HÖRNBLAD

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

131. Mellbin, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw. kr. 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw. kr. 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951 with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr. 25.— 1962
134. Möller, Tage, Shunt Operations in Morbus [illegible]. Results in 161 Cases and Clinical Follow-up. Sw. kr. 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw. kr. 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr. 25.— 1962
137. Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr. 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr. 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wase-Hückert, Ole and Donner, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr. 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr. 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr. 25.— 1963
147. Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children, Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr. 20.— 1963
149. Valaes, Timos, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr. 25.— 1963
150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics, Lisbon, 1962.* Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil [illegible] in Newborns. A Clinical and Cytogenetic Study. [illegible]
155. [illegible] Studies in Children. XI. Mechanics of Breat[illegible] and Ventilatory Capacity in Asthmatic C[illegible] to Symptom-free Status. Sw. kr. 25.— [illegible]
156. *Nils* [illegible] *his Textbook on Paediatrics.* Edited [illegible] Wallgren. Sw. kr. 25.— 1964
157. Bro[illegible] [illegible] 15 [illegible] dersen, P. A., Glycogenosis Type [illegible] phatase) in Four Siblings. Sw. kr. [illegible]
158. A[illegible] in the Newborn Infant. Sw. kr. 25.—
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm. 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Ockerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Pelmann, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children. Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A Morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chernub.* Sw. kr. 15.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Olov, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hänninen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen 1967. Sw. kr. 15.— 1967
178. Sjögren, Inken, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Gösta, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Else, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1969
188. Meeuwisse, Gunnar W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Häggblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Kelvikko, Antti, Cardiovascular Responses of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969

kr 30.—

[illegible] ver printed in [illegible] & Wiksells Boktryckeri AB Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 190 1969

EXPERIMENTAL STUDIES ON CLOSURE OF THE DUCTUS ARTERIOSUS UTILIZING WHOLE-BODY FREEZING

BY P YNGVE HÖRNBLAD

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Paediatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

131 Mellbin, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw. kr. 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw. kr. 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr. 25.— 1962
134. Möller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr. 25.— 1962
135. *I Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet, June 30, 1962.* Sw. kr. 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and clinical, psychological and electroencephalographic comparison between children ith migraine and matched controls. Sw. kr. 25.— 1962
137 Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr. 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children ith Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr. 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr. 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen, 1961. Edited by E. Winge Flensborg. Sw. kr. 30.— 1963
141. Wasz-Höckert, Ole and Donner, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr. 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr. 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr. 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr. 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *I Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr. 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr. 25.— 1963
148. Bergen, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr. 20.— 1963
149. Valaes, Tamas, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr. 25.— 1963
150. Mac, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151 *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics,* Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study. Sw. kr. 30.— 1964
155. Engström, Inga, atory Studies in Children. XI. Mechanics of Breathing, e and Ventilatory Capacity in Asthmatic Child to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén* *Textbook on Paediatrics.* Edited by Bo allgren. Sw. kr. 25.— 1964
157 Brante, rman, P. A., Glycogenosis Type 1 (Lac ase) in Four Siblings. Sw. kr. 15.—
158. A the Newborn Infant. Sw. kr. 25.— 196
159. *Proceedings of the Fourteenth Northern Paediatric Congress* Stockholm. 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Ockerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Polosa, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H. Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
167 Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children. Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A Morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chenaud.* Sw. kr. 15.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Olov, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hänninen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177 *Proceedings of the Fifteenth Northern Paediatric Congress.* Bergen. 1967. Sw. kr. 35.— 1967
178. Sjögren, Irene, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using a Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181 Koch, Günter, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F., and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Else, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187 Karlberg, Petter, *et al.*, The Development of Children in Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1969
188. Mossewitsch, Gunnar W., and Mellin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Härnblad, F. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191 Kelvikio, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969

Pr ed. kr 30 —

r printed by [illegible] & Wiksells Boktryckeri AB, Uppsala

CONTENTS

The present dissertation is a summary of the following papers

I Hörnblad, P. Y. & Larsson K. S. Studies on closure of the ductus arteriosus. I. Whole body freezing as improvement of fixation procedures. *Cardiologia (Basel) 51*: 231, 1967

II Hörnblad P. Y. & Larsson, K. S. Studies on closure of the ductus arteriosus. II. Closure rate in the rat and its relation to environmental temperature. *Cardiologia (Basel) 51*: 242, 1967

III Hörnblad P. Y. Studies on closure of the ductus arteriosus. III. Species differences in closure rate and morphology. *Cardiologia (Basel) 51*: 262, 1967

IV Hörnblad P. Y. Embryological observations of the ductus arteriosus in the guinea pig, rabbit, rat and mouse. Studies on closure of the ductus arteriosus. IV. *Acta Physiol Scand* 1969 (in press)

V Hörnblad P. Y. & Friberg U. Studies on closure of the ductus arteriosus. V. Microradiographical observations with ultrasoft X rays on closure of the ductus arteriosus in the rat and the guinea pig. *Acta Path Microbiol Scand* 1969 *(in press)*

VI Hörnblad P. Y. Effect of oxygen and umbilical cord clamping on closure of the ductus arteriosus in the guinea pig and the rat. Studies on closure of the ductus arteriosus. VI. *Acta Physiol Scand* 1969 (in press)

Reference will be made to these papers using the Roman figures as listed above

CONTENTS

INTRODUCTION

The direct communication between the pulmonary trunk and the aorta in the foetus is known as the ductus arteriosus. Although this structure was described by Galen as early as the second century A. D its function was not known until Harvey in 1628 introduced the modern concept of the blood corculation (8) In the foetus, the ductus arteriosus permits blood from the right ventricle to enter the systemic circulation without passing through the lungs. It is of great importance that the circulation through the ductus is arrested after birth to establish complete separation of the pulmonary circulation from the systemic. This is mediated by closure of the ductus a process which is not fully understood In human beings, the ductus exceptionally fails to close resulting in a condition which is known as a patent or persistent ductus arteriosus. Its aetiology is still unknown but it is interesting to note that it is not infrequently associated with other malformations (63) Even if a patent ductus arteriosus can nowadays be corrected surgically at a low risk (22) it is highly desirable to diminish its incidence. A prerequisite is, however to obtain further basic information about the ductal morphology and physiology which can only be achieved experimentally

SURVEY OF THE LITERATURE

In this section the most pertinent literature on closure of the ductus arteriosus will be briefly surveyed. For more comprehensive reviews, reference is made to publications by Swensson (84) Sciacca & Condorelli (78) and van Ingen (42)

Morphology of the ductus arteriosus

The ductus arteriosus in human beings was early found to differ morphologically from the aorta and the pulmonary trunk (48) The full term ductus has frequently been ascribed a thick, loose wall in comparison to the aorta, with a narrowed lumen lined by a prominent intima exhibiting protrusions (7 28 38 43 84) Its nature of a muscular artery (12) is now generally accepted. A similar ductal morphology has been described in the guinea pig (45 65) rat (42 60) and rabbit (80) Fixation procedures have occasionally been suggested to cause artefacts of the ductal morphology (6 65 88) In an attempt to diminish these artefacts by distension of ductuses from autopsy cases during the fixation period, a very thin wall an inconsiderable intima without protrusions, and a rounded lumen were found (6)

Mode of ductal closure

Closure of the ductus arteriosus has been described as an initial passive phenomenon, succeeded by proliferative processes of the wall Compression of the ductus was one of the explanations of its passive closure (53 59 Kinking and twisting of the ductus has also been suggested to cause closure (51 77 A valve like formation of the ductus has been stated to provide an instantaneous arrest of the blood flow (71 83) However closure of the ductus has also been reported to result from proliferative processes—occuring already prenatally—

without preliminary passive occlusion (38, 48, 78).

According to the current concept, closure of the ductus arteriosus can be divided into two distinct phases (8, 45, 58). The primary phase consists of a contraction of the ductal wall with narrowing of the lumen, and the secondary phase of an intimal proliferation causing final obliteration. These phases are usually denoted as the physiological and the anatomical closure, respectively, arising from the terms which Gérard (27) introduced in 1900: "l'occlusion physiologique" and "l'oblitération anatomique". However, Gérard believed the physiological closure to be passive. As early as 1856, Virchow (87) put forward the hypothesis that an active muscular contraction of the ductal wall was responsible for an early closure. Von Hayek (34) and later Meyer & Simon (56) made a detailed study of the morphological prerequisites for muscular contraction. It is generally agreed that the anatomical phase of ductal closure consists of intimal proliferation, degeneration and atrophy of muscular elements with subsequent sclerosis (38, 43, 62). Augmentation of elastic tissue (43, 76) and deposition of mucoid substances (38, 42, 78, 86) are other factors which have been ascribed crucial importance.

Rate of ductal closure

The concept ductal closure rate has not been used earlier since the reduction in the ductal lumen has not been examined at regular and frequent intervals after birth. In morphological studies, the time after birth for closure of the ductus has been determined from disappearance of the lumen. In physiological studies, on the other hand, closure of the ductus has been considered to exist when arrest of the blood flow was observed.

Closure of the human ductus was believed to occur instantaneously on birth, when mechanical factors were suggested to be responsible for passive closure (51, 53, 59, 71, 77, 83). A closure process over a long period has on the contrary been reported when intimal proliferation alone was proposed to cause closure (38, 48). Physiological studies in human beings have also indicated that blood may flow through the ductus for several days after birth (4, 16, 23, 50, 72). Reports of a rapid closure, based on morphological investigations in the guinea-pig (45), rat (42) and rabbit (80) and on physiological studies in the lamb (8), support the view of a muscular contraction of the wall. Contrarily, a considerable blood flow through the ductus has been demonstrated in physiological investigations for up to 2 days in the lamb (21), calf and foal (1) and during the first day in the dog (25). In the guinea-pig as well, late closure has been observed morphologically (37, 65).

Anatomical closure has been reported to be complete in one up to several months in human beings (38, 43, 53, 62). Similar periods are given in the pig (76) and calf (33). In the dog (39), cat (40), guinea-pig (45) and rat (42) complete obliteration has been noted 1—4 weeks after birth.

Cause of ductal closure

The common cause of different modes of a passive ductal closure has been ascribed to the onset of respiration. Displacement of mediastinal organs was considered to cause compression (53, 59), kinking and twisting of the ductus (51, 77), and the ductal valve (71, 83) was believed to close under the influence of haemodynamic changes. Aeration of the lungs has also been regarded to produce lowering of the distension pressure in the ductus, which would simply enable the distended ductal wall to contract (70).

The discussed causes of an active contraction of the ductal wall do not have a common denominator. Stimulation of the left vagus nerve has been used to elicit ductal contraction in the guinea-pig (9). Nearly 30 years ago, good evidence of a relation between oxygen and ductal closure was presented by Kennedy & Clark (45, 46). An increase in oxygen saturation of the

INTRODUCTION

The direct communication between the pulmonary trunk and the aorta in the foetus is known as the ductus arteriosus. Although this structure was described by Galen as early as the second century A D its function was not known until Harvey in 1628 introduced the modern concept of the blood corculation (8) In the foetus the ductus arteriosus permits blood from the right ventricle to enter the systemic circulation without passing through the lungs. It is of great importance that the circulation through the ductus is arrested after birth to establish complete separation of the pulmonary circulation from the systemic This is mediated by closure of the ductus, a process which is not fully understood. In human beings, the ductus exceptionally fails to close resulting in a condition which is known as a patent or persistent ductus arteriosus. Its aetiology is still unknown but it is interesting to note that it is not infrequently associated with other malformations (63) Even if a patent ductus arteriosus can nowadays be corrected surgically at a low risk (22) it is highly desirable to diminish its incidence. A prerequisite is, however to obtain further basic information about the ductal morphology and physiology which can only be achieved experimentally

SURVEY OF THE LITERATURE

In this section the most pertinent literature on closure of the ductus arteriosus will be briefly surveyed For more comprehensive reviews reference is made to publications by Svensson (84) Sciacca & Condorelli (78) and van Ingen (42)

Morphology of the ductus arteriosus

The ductus arteriosus in human beings was early found to differ morphologically from the aorta and the pulmonary trunk (48) The full term ductus has frequently been ascribed a thick, loose wall in comparison to the aorta, with a narrowed lumen lined by a prominent intima exhibiting protrusions (7 28 38 43 84) Its nature of a muscular artery (12) is now generally accepted. A similar ductal morphology has been described in the guinea pig (45 65) rat (42 60) and rabbit (80) Fixation procedures have occasionally been suggested to cause artefacts of the ductal morphology (6 63 88) In an attempt to diminish these artefacts by distension of ductuses from autopsy cases during the fixation period, a very thin wall an inconsiderable intima without protrusions, and a rounded lumen were found (6)

Mode of ductal closure

Closure of the ductus arteriosus has been described as an initial passive phenomenon, succeeded by proliferative processes of the wall Compression of the ductus was one of the explanations of its passive closure (53 59 Kinking and twisting of the ductus has also been suggested to cause closure (51 77 A valve like formation of the ductus has been stated to provide an instantaneous arrest of the blood flow (71 83) However closure of the ductus has also been reported to result from proliferative processes—occuring already prenatally—

without preliminary passive occlusion (38, 48, 78).

According to the current concept, closure of the ductus arteriosus can be divided into two distinct phases (8, 45 58). The primary phase consists of a contraction of the ductal wall with narrowing of the lumen, and the secondary phase of an intimal proliferation causing final obliteration. These phases are usually denoted as the physiological and the anatomical closure, respectively arising from the terms which Gérard (27) introduced in 1900 "l'occlusion physiologique" and "l'oblitération anatomique". However Gérard believed the physiological closure to be passive. As early as 1856, Virchow (87) put forward the hypothesis that an active, muscular contraction of the ductal wall was responsible for an early closure. Von Hayek (34) and later Meyer & Simon (56) made a detailed study of the morphological prerequisites for muscular contraction. It is generally agreed that the anatomical phase of ductal closure consists of intimal proliferation, degeneration and atrophy of muscular elements with subsequent sclerosis (38, 43, 62). Augmentation of elastic tissue (53, 76) and deposition of mucoid substances (38 42, 78, 86) are other factors which have been ascribed crucial importance.

Rate of ductal closure

The concept ductal closure rate has not been used earlier since the reduction in the ductal lumen has not been examined at regular and frequent intervals after birth. In morphological studies, the time after birth for closure of the ductus has been determined from disappearance of the lumen. In physiological studies, on the other hand, closure of the ductus has been considered to exist when arrest of the blood flow was observed.

Closure of the human ductus was believed to occur instantaneously on birth, when mechanical factors were suggested to be responsible for a passive closure (51 53, 59 71 77 83). A closure process over a long period has, on the contrary, been reported when intimal proliferation alone was proposed to cause closure (38, 48). Physiological studies in human beings have also indicated that blood may flow through the ductus for several days after birth (2, 16 23, 50, 72). Reports of a rapid closure, based on morphological investigations in the guinea-pig (45) rat (42) and rabbit (60) and on physiological studies in the lamb (8) support the view of a muscular contraction of the wall. Contrarily a considerable blood flow through the ductus has been demonstrated in physiological investigations for up to 2 days in the lamb (21) calf and foal (1) and during the first day in the dog (25). In the guinea-pig as well, late closure has been observed morphologically (32 65).

Anatomical closure has been reported to be complete in one up to several months in human beings (38, 43 53 62). Similar periods are given in the pig (76) and calf (33). In the dog (39) cat (40) guinea-pig (45) and rat (42) complete obliteration has been noted 1—4 weeks after birth.

Cause of ductal closure

The common cause of different modes of a passive ductal closure has been ascribed to the onset of respiration. Displacement of mediastinal organs was considered to cause compression (53 59). Kinking and twisting of the ductus (51 77) and the ductal valve (71 83) was believed to close under the influence of haemodynamic changes. Aeration of the lungs has also been regarded to produce lowering of the distension pressure in the ductus which would simply enable the distended ductal wall to contract (70).

The discussed causes of an active contraction of the ductal wall do not have a common denominator. Stimulation of the left vagus nerve has been used to elicit ductal contraction in the guinea-pig (9). Nearly 30 years ago, good evidence of a relation between oxygen and ductal closure was presented by Kennedy & Clark (45, 46). An increase in oxygen saturation of the

blood perfusing the ductus in the lamb was later shown to cause a contraction of its wall, whereas a decrease in oxygen saturation caused dilatation of a partially contracted ductus (3 10 68) Additional support for the role of oxygen is obtained by the fact that the physiological closure is affected only by a reduced oxygen supply Administration of nitrogen has resulted in failure of the guinea pig ductus to close or reopening of a partially closed ductus *in vivo* (46) and *in vitro* (47) Similarly under hypoxia, a delay in ductal closure has been reported in the guinea pig (67) and dog (88) and widening of the ductus has been described in the lamb (10) and the human being (44 57)

It has, on the other hand, been stated that the ductus will also contract at a low saturation during asphyxia (10) Liberated catecholamines have been suggested to cause closure of the ductus in this condition. Administration of catecholamines has also been demonstrated to cause constriction of the lamb ductus, both *in vivo* (10) and *in vitro* (47) A direct effect of catecholamines on the ductus *in vivo* has nevertheless also been denied (79)

Considerable interest has been focused on kinins in adaptation of the circulation to extrauterine life (54 74) Recently it has been demonstrated that bradykinin is very potent in causing constriction of the calf and lamb ductus arteriosus *in vitro* (24)

An interference with the anatomical closure seems to occur when newborn rats are treated with aminoacetonitrile (41)

PRESENT INVESTIGATIONS

OBJECT OF THE STUDIES

It is obvious from the reviewed literature that different concepts still exist concerning the ductal morphology as well as the mode and time of physiological closure of the ductus arteriosus. Moreover no conclusive cause of the physiological closure has been presented.

Consequently it seemed expedient to perform additional studies on closure of the ductus arteriosus. The present investigations were strictly limited to experimental studies of the physiological phase, and the aims were

1. To apply a morphological technique which allows instantaneous and permanent immobilization of the ductus arteriosus.
2. To study the mode of ductal closure in different species on the basis of morphological changes occurring prenatally and at birth.
3. To determine the rate of ductal closure in different species.
4. To study the cause of ductal closure by means of interference with the physiological phase of closure in different species.

METHODOLOGICAL

Animals

In the present investigations, experimental animals of five species were used: pig (III), guinea-pig (III—VI), rabbit (III, IV), rat (I—VI) and mouse (III, IV). All these species—except the mouse—have been studied in earlier investigations of the ductus arteriosus. Comparisons with earlier results were therefore possible. Moreover the selected species exhibit a different degree of development at birth, with respect to e. g. maturity of the nervous system, locomotor organs and temperature regulation.

All animals were obtained from commercial suppliers, except for the mice which were inbred at the laboratory (49).

Animals housed in the laboratory were fed on standardized diets (I, III). In the rat and mouse pregnancy was diagnosed from the presence of sperms in the vaginal smear and finding of a vaginal plug, respectively (I, III). In the pig and rabbit, the day of mating was given by the supplier. The time of mating of the guinea-pigs used in the embryological experiment (IV) was established to within two days. Accurate embryonic age was thus secured for the prenatal study (IV) and facilitated predicting the time of delivery in the other experiments (I—III, V, VI). Guinea-pigs with known date of mating were not, however, available in adequate numbers for the investigation on the material submitted to caesarean section near term (VI). The method of determining approaching delivery by observing the degree of symphysiolysis (66) proved to be satisfactory.

Experimental procedures

In the studies on the closure rate (II, III) and the morphology postnatally (II, III, V) the newborns were kept under conditions which can be considered as applying in nature. In the pig and guinea-pig, this was ensured by allowing the mothers to nurture the newborns at room

blood perfusing the ductus in the lamb was later shown to cause a contraction of its wall, whereas a decrease in oxygen saturation caused dilatation of a partially contracted ductus (3 10 68) Additional support for the role of oxygen is obtained by the fact that the physiological closure is affected only by a reduced oxygen supply Administration of nitrogen has resulted in failure of the guinea pig ductus to close or reopening of a partially closed ductus *in vivo* (46) and *in vitro* (47) Similarly under hypoxia, a delay in ductal closure has been reported in the guinea pig (67) and dog (88) and widening of the ductus has been described in the lamb (10) and the human being (44 57)

It has on the other hand been stated that the ductus will also contract at a low saturation during asphyxia (10) Liberated catecholamines have been suggested to cause closure of the ductus in this condition. Administration of catecholamines has also been demonstrated to cause constriction of the lamb ductus, both *in vivo* (10) and *in vitro* (47) A direct effect of catecholamines on the ductus *in vivo* has nevertheless also been denied (79)

Considerable interest has been focused on kinins in adaptation of the circulation to extra uterine life (54 74) Recently it has been demonstrated that bradykinin is very potent in causing constriction of the calf and lamb ductus arteriosus *in vitro* (24)

An interference with the anatomical closure seems to occur when newborn rats are treated with aminoacetonitrile (41)

PRESENT INVESTIGATIONS

OBJECT OF THE STUDIES

It is obvious from the reviewed literature that different concepts still exist concerning the ductal morphology as well as the mode and time of physiological closure of the ductus arteriosus. Moreover no conclusive cause of the physiological closure has been presented.

Consequently it seemed expedient to perform additional studies on closure of the ductus arteriosus. The present investigations were strictly limited to experimental studies of the physiological phase, and the aims were

1. To apply a morphological technique which allows instantaneous and permanent immobilization of the ductus arteriosus.
2. To study the mode of ductal closure in different species on the basis of morphological changes occurring prenatally and at birth.
3. To determine the rate of ductal closure in different species.
4. To study the cause of ductal closure by means of interference with the physiological phase of closure in different species.

METHODOLOGICAL

Animals

In the present investigations, experimental animals of five species were used pig (III) guinea-pig (III—VI) rabbit (III IV) rat I—VI) and mouse (III IV) All these species —except the mouse—have been studied in earlier investigations of the ductus arteriosus. Comparisons with earlier results were therefore possible. Moreover the selected species exhibit a different degree of development at birth, with respect to e g maturity of the nervous system, locomotor organs and temperature regulation.

All animals were obtained from commercial suppliers, except for the mice, which were inbred at the laboratory (49)

Animals housed in the laboratory were fed on standardized diets (I, III) In the rat and mouse, pregnancy was diagnosed from the presence of sperms in the vaginal smear and finding of vaginal plug, respectively (I III) In the pig and rabbit, the day of mating was given by the supplier The time of mating of the guinea-pigs used in the embryological experiment (IV) was established to within two days. Accurate embryonic age was thus secured for the prenatal study (IV) and facilitated predicting the time of delivery in the other experiments (I—III V VI) Guinea-pigs with known date of mating were not, however available in adequate numbers for the investigation on the material submitted to caesarean section near term (VI) The method of determining approaching delivery by observing the degree of symphysiolysis (66) proved to be satisfactory

Experimental procedures

In the studies on the closure rate (II, III) and the morphology postnatally (II III V) the newborns were kept under conditions which can be considered as applying in nature. In the pig and guinea-pig, this was ensured by allowing the mothers to nurture the newborns at room

temperature until sacrifice. This could not be done in the rabbit, rat and mouse as these species—when disturbed during delivery—will not nurture their offspring and may even injure the newborns. To prevent the loss of body temperature in newborn rats and mice (26 36) they were placed in glass tubes incubated at 37 C and 36°C, respectively which is close to the normal body temperature of adult rats and mice (29) Newborn rabbits were brought to an incubator at 30°C although the body temperature of adult animals is close to 39°C (29) As rabbits normally deliver out-of-doors, it was considered that the temperature would have been lower in the burrow

Caesarean section was always performed under ether anaesthesia (IV VI) General anaesthesia could be kept superficial for up to 1 hour by the addition of a local anaesthetic in the abdominal wall (VI)

The effect of hypothermia on the ductal closure rate was studied in the rat (II) The newborns were placed in ventilated glass tubes, which were incubated at 37 C, 30°C and 21 C The animals were sacrificed at the age of 4 hours, or at definite intervals earlier —To study the influence of hypoxia on the ductal closure rate (VI) newborn rats were kept in glass tubes at 37 C in an atmosphere of 8 ± 1 per cent of oxygen in nitrogen, while control animals were allowed to breathe air They were sacrificed at definite intervals up to 4 hours. — To determine the effect of inhaled air and nitrogen on closure of the ductus arteriosus in the guinea pig (VI) full term foetuses were delivered by caesarean section under lukewarm saline They were raised to the surface and allowed to breathe air or supplied with nitrogen in an inverted glass funnel for periods of 5 minutes before sacrifice

The effect on the heart rate of hypothermia (II) and hypoxia (VI) was studied in the rat Newborns were incubated in glass tubes, and by means of special electrodes, electrocardiographic recordings were made at 15 minute intervals during 4 hours after birth. The heart rate was determined from 10 consecutive heart cycles.

Sacrifice was performed by whole body freezing (I) of all animals used in investigations II—VI In addition to animals sacrificed immediately on birth newborns of the pig were sacrificed at intervals of up to 24 hours after birth, those of the guinea pig up to 12 hours, and those of the rabbit, rat and mouse at intervals up to 4 hours after birth Newborns of the rat and mouse were frozen in isopentane cooled by dry ice (—78 C 30) Newborn pigs, guinea pigs and rabbits were frozen in liquid nitrogen (—196 C 30) as it was very inconvenient to cool isopentane in amounts necessary for their effective freezing Dislocation of the atlas, followed by freezing or ordinary formalin fixation after storage or after dissecting out the ductus, was also used for comparisons between different fixation techniques (I)

Freeze fixation was obtained simultaneously after whole body freezing which allowed transfer of cryostat sections to slides with the original structure of the tissues preserved. The morphology of the freeze-fixed tissue was satisfactory as no freezing artefacts could be observed in the light microscope.— A series of sections at close intervals was prepared throughout the ductus, in addition to sample sections. The series was well stained in haematoxylin and eosin. Selected sections were successfully stained for elastic fibres in Weigert's resorcin fuchsin, and the collagen fibres were visualized in Masson's trichrome stain (17) —Cryostat sections were also used for the microradiographical investigations (V) by affixing them to celloidin-coated Eastman Kodak High Resolution Plates. These were exposed at 1 2—1 6 kV and developed in Kodak D19b Only qualitative analysis under the light microscope was made

Microscopical examination of the ductal morphology was undertaken, and the dimensions of the lumen and wall thickness of the ductus were recorded (I—VI) The section of the ductus arteriosus showing the smallest lumen was selected for microscopical measurements of the outer and inner diameters. The measurements were made at the narrowest point of the lumen and in the plane perpendicular to the narrowest

point. The arithmetic means of these measurements w re used for calculation of mean values of inner diameter and wall thickness in the different experimental groups. All dimensions were determined under the light microscope using a measuring eye-piece. This allowed measurements of the ductus in the pig guinea pig and rabbit to be made w th a precision of $\pm 20\ \mu$, and in the rat and mouse of $\pm 8\ \mu$. Tabulated mean alues of inner diameter nd wall thickness were rounded off to the nearest 10 μ in the pig, guinea-pig and rabbit, and to the nearest 5 μ in the rat and mouse.

For comparisons between the different species with respect to the degree of ductal closure use was made of the ratio mean alue of the wall thickness to the inner diameter of the ductus — $\frac{\text{wall thickness}}{\text{inner diameter}}$ (III IV VI) This ratio was also used as a complement to com parisons between the mean inner diameter in the different experimental groups within one pecies (VI)

For statistical comparisons between the mean alues in the different experimental groups, a one-tailed analysis of "Student s t test (61) was performed. In all investigations, the experimental groups were provided with animals in a regular order to obtain an even distribution of possible ariations within the litters.

RESULTS

Efficiency of whole-body freezing

When whole-body freezing (I) was used for sacrifice and fixation (II—VI) the central essels displayed a wide, rounded lumen with a smooth inner surface, which was lined by widely separated flat endothelial cells. The thin media was composed of straight elastic lamellas and interposed lender muscle cells. This was in striking contrast to the ascular morphology after formalin fixation (I) which was charac terized by deformed and narrowed lumen, lined by thick, closely packed endothelial cells, and a broad media showing pronounced w ness of the elastic lamellas and thick cells in between. Particularly the ductus arteriosus of newborns exhibited—when fixed in formalin or subjected t mechanical stimulation (I)—severe distortions as described above, which were not observed after whole-body freezing

The ductal morphology seen after whole-body freezing revealed, moreover that considerable differences were present shortly after birth, whereas the morphology of the aorta and pulmonary trunk was unchanged (II III) This difference could be demonstrated within few minutes of birth in the guinea-pig and rabbit.

Morphological observations on the ductus arteriosus

At birth the ductus arteriosus of whole-body frozen animals showed, in all five species, rounded lumen with a smooth inner surface lined by a single layer of flat endothelial cells (I—III V VI) The subendothelial zone was of inappreciable extent in the rat and mouse, whereas in the pig, guinea-pig and rabbit, fibroblasts and elastic and collagen fibres were isible most prominent in the rabb t. The media was composed of straight elastic lamellas, alternat ing with thin layers of slender smooth muscle cells and occasional fibroblasts. The number of lamellas aried with the pecies, but was fairly constant within the species (III) The inner and outer parts of the media had the same dry mass concentration (V) No distinct ad entitia could be separated from the surrounding loose connectiv tissue. This layer was therefore ex cluded when the wall thickness was measured.

Comparisons between the ratio $\frac{\text{wall thickness}}{\text{inner diameter}}$ revealed that newborns of the pig, guinea pig and rat had the same relative wall thickness of 0.07 (III) Newborns of the rabbit had a higher

temperature until sacrifice. This could not be done in the rabbit, rat and mouse as these species—when disturbed during delivery—will not nurture their offspring and may even injure the newborns. To prevent the loss of body temperature in newborn rats and mice (26, 36) they were placed in glass tubes incubated at 37°C and 36°C respectively which is close to the normal body temperature of adult rats and mice (29) Newborn rabbits were brought to an incubator at 30°C although the body temperature of adult animals is close to 39°C (29) As rabbits normally deliver out-of-doors, it was considered that the temperature would have been lower in the burrow

Caesarean section was always performed under ether anaesthesia (IV VI) General anaesthesia could be kept superficial for up to 1 hour by the addition of a local anaesthetic in the abdominal wall (VI)

The effect of hypothermia on the ductal closure rate was studied in the rat (II) The newborns were placed in ventilated glass tubes, which were incubated at 37°C, 30°C and 21°C. The animals were sacrificed at the age of 4 hours or at definite intervals earlier —To study the influence of hypoxia on the ductal closure rate (VI) newborn rats were kept in glass tubes at 37 C in an atmosphere of 8 ± 1 per cent of oxygen in nitrogen, while control animals were allowed to breathe air They were sacrificed at definite intervals up to 4 hours. — To determine the effect of inhaled air and nitrogen on closure of the ductus arteriosus in the guinea pig (VI) full term foetuses were delivered by caesarean section under lukewarm saline They were raised to the surface and allowed to breathe air or supplied with nitrogen in an inverted glass funnel for periods of 5 minutes before sacrifice

The effect on the heart rate of hypothermia (II) and hypoxia (VI) was studied in the rat. Newborns were incubated in glass tubes, and by means of special electrodes, electrocardiographic recordings were made at 15-minute intervals during 4 hours after birth The heart rate was determined from 10 consecutive heart cycles.

Sacrifice was performed by whole-body freezing (I) of all animals used in investigations II—VI In addition to animals sacrificed immediately on birth newborns of the pig were sacrificed at intervals of up to 24 hours after birth, those of the guinea pig up to 12 hours, and those of the rabbit, rat and mouse at intervals up to 4 hours after birth Newborns of the rat and mouse were frozen in isopentane cooled by dry ice (—78°C 30) Newborn pigs, guinea-pigs and rabbits were frozen in liquid nitrogen (—196 C 30) as it was very inconvenient to cool isopentane in amounts necessary for their effective freezing Dislocation of the atlas, followed by freezing or ordinary formalin fixation after storage or after dissecting out the ductus, was also used for comparisons between different fixation techniques (I)

Freeze fixation was obtained simultaneously after whole-body freezing which allowed transfer of cryostat sections to slides with the original structure of the tissues preserved. The morphology of the freeze-fixed tissue was satisfactory as no freezing artefacts could be observed in the light microscope.—A series of sections at close intervals was prepared throughout the ductus, in addition to sample sections. The series was well stained in haematoxylin and eosin. Selected sections were successfully stained for elastic fibres in Weigert's resorcin fuchsin, and the collagen fibres were visualized in Masson's trichrome stain (17) —Cryostat sections were also used for the microradiographical investigations (V) by affixing them to celloidin-coated Eastman Kodak High Resolution Plates. These were exposed at 1 2—1 6 kV and developed in Kodak D19b. Only qualitative analysis under the light microscope was made

Microscopical examination of the ductal morphology was undertaken and the dimensions of the lumen and wall thickness of the ductus were recorded (I—VI) The section of the ductus arteriosus showing the smallest lumen was selected for microscopical measurements of the outer and inner diameters. The measurements were made at the narrowest point of the lumen and in the plane perpendicular to the narrowest

umbilical circulation were kept for 5 minutes in nitrogen after an initial period in air (VI)

In the rat, a significant delay in the ductal closure rate was recorded when newborns were kept in atmosphere of reduced oxygen concentration (VI) or when the environmental temperature was lowered to 21 C (II) In animals 4 hours of age, the lumen was nevertheless reduced to less than 5 per cent. A decrease in the environmental temperature to 30°C did not affect the closure rate (II) On the other hand, the observed decrease in the heart rate under hypothermia (II) showed an almost linear correlation to the environmental temperature A significantly depressed heart rate was also recorded under hypoxia (VI)

DISCUSSION

Whole-body freezing in studies of the ductus arteriosus

The blood shunt through the ductus arteriosus at different stages of ductal closure has been studied as a part of foetal adaptation to extrauterine life. Different techniques have been used, such as direct measurements of the blood flow (4) blood oxygen analyses (23 58) cineradiography (8) dye dilution (16, 31 64) and isotope tracing (25)

For studies of the ductal closure *per se* on the other hand, it is appropriate to record the changes in the ductal lumen by direct measurements of its inner diameter Until whole-body freezing was used for sacrifice and fixation, it was not possible to visualize the ductus arteriosus in a state which might reflect its state *in vivo* (I) The commonly used technique of immersion fixation after death—preceded in most cases by dissection—is ineffective, as post mortem contraction of the wall cannot be prevented (I) The risk of fixation artefacts has been apprehended, but the attempts to avoid them by refrigeration and delayed fixation (65 88 were doomed to failure (52) Although distension of the ductus prior to fixation (6) will improve its morphology reliable information about its dimensions cannot be obtained, because of possible overdistension (55) After whole-body freezing, on the contrary it has been demonstrated that the ductus arteriosus of various species exhibits characteristics of vessels distended under pressures which can be considered as physiological (13 15 55 69) Moreover the finding in newborns of the guinea-pig and rabbit of very rapid changes in the ductal inner diameter (III) indicates that instantaneous immobilization of the ductus is achieved by this technique. Since the ductus cannot be considered to freeze instantaneously even in such small animal as the newborn mouse the intraluminal pressure seems to be maintained in an unspecified way until the ductal wall is frozen. The results in the pig indicate that the efficiency of whole-body freezing is not limited by the size of the animals used in this study This implies that reliable information about actual dimensions of the ductus arteriosus before birth and during its closure can be obtained in different species Minute deviations from the normal closure process, *e g* induced by experimental factors, can also be visualized by use of the whole-body freezing technique.

Mode of ductal closure

Observations of decreased outer diameter and increased wall thickness, accompanied by w ness of the elastic lamellas, remodelling of the inner media and central displacement of the intima (II III) support the generally accepted view that the ductus arteriosus is closed by a muscular contraction of its wall after birth (6, 8, 33 42, 57 62, 82)

The present observation of a progressive growth of the ductal *lumen during late* intrauterine life in four species (IV) is contrary to reports of a constant lumen during this period

value, but in some of these animals closure was already initiated (III) Full term rabbit foetuses, on the other hand also exhibited a relative wall thickness of 0 07 (IV) In the mouse, the newborns (III) had a value of only 0 04 which, moreover was close to the value of 0 03 found in the rat aorta (IV) In the mouse the ductus and the aorta also displayed similar amounts of elastic fibres, whereas in the other four species, the ductal wall contained definitely less elastic tissue than the aorta (III)

During closure the ductus arteriosus in all five species exhibited similar morphological changes, which moreover were directly correlated to the degree of closure (II III) With narrowing of the lumen the outer diameter decreased and the wall gained in thickness. At the inner surface the endothelial cells piled up and the media displayed progressive remodelling The elastic lamellas showed increasing waviness and condensation most marked centrally This was very strikingly visualized in the microradiograms (V) The interposed cells became thicker and their circular orientation was changed to a radial one in the inner part of the media No concomitant change in dry mass concentration was observed (V) During closure, the ductal lumen of the pig guinea pig and rabbit became deformed by indentations of the wall, indicative of advanced remodelling This was most conspicuous in the ductus of the guinea pig in which tissue defects in the inner media were easily identifiable in ordinary histological sections (III) as well as in microradiograms (V) In completely occluded ductuses of all species, the endothelial cells were accumulated centrally with formation of a solid cell core In addition to other intimal structures, they filled up the rounded or slit like space available inside the constricted media.

Prenatally during the last part of intrauterine life, an increase in the ductal lumen was found in the guinea pig rabbit rat and mouse, whereas an increase in wall thickness could be demonstrated only in the guinea pig and the rabbit (IV) The structure of the wall did not change during this phase and the ductal morphology of full term foetuses (IV) was indistinguishable from that of newborn animals (III) Dimensions of inner diameter and wall thickness were also of the same magnitude in full term foetuses (IV) and in newborns (III)

Rate of ductal closure

Investigations of the ductal closure rate disclosed that species differences existed (II III) Newborns of the guinea pig and rabbit showed very rapid closure of the ductus a narrowing of the lumen to less than 5 per cent could be demonstrated after 2 minutes. Newborns of the pig rat and mouse showed no such instantaneous closure. In the mouse a corresponding narrowing of the ductal lumen was found after 30 minutes, in the rat only after 1 hour and newborns of the pig did not exhibit the same degree of closure until ? hours after birth. In the guinea pig and rabbit, complete occlusion of the ductus followed about 30 minutes after birth, while in the mouse disappearance of the lumen was demonstrated only after 2 hours, in the rat after 3 hours and in the pig after 8 hours. Also in the mouse a significant reduction in the ductal lumen was observed at the age of 2 minutes. In the rat, on the other hand, no decrease occurred during the first 10 minutes following birth (III)

Interference with the physiological phase of ductal closure

Closure of the ductus arteriosus could be affected by means of certain experimental conditions (II VI) In the guinea pig closure was prevented by keeping foetuses—with intact or interrupted umbilical circulation—in an atmosphere of nitrogen (VI) Narrowing of the ductal lumen to about ?0 per cent occurred, on the other hand within 5 minutes in foetuses with an intact umbilical circulation when kept in air and to approximately ? per cent when the umbilical circulation was interrupted. No significant dilatation of a partially closed ductus was obtained when foetuses with an interrupted

Cause of ductal closure

Of factors which have proved to induce constriction of the ductus (9 10, 4 45 46, 47 79) only oxygen and certain vasoactive agents might be relevant in discussing causes of the physiological ductal closure.

The present results (VI) confirm that oxygen causes ductal closure in the guinea-pig (45). Furthermore, the observed delayed closure rate in rats under hypoxia supports the role of oxygen in ductal closure (VI). The mechanism of oxygen action is not, however satisfactorily explained. Its effect has been suggested to be mediated by rise in the oxygen saturation of the blood perfusing the ductus (5 10, 46, 57 68). This implies that a reverse shunt through the ductus is initially established, a condition which has been demonstrated in the lamb (20) calf and foal (1). Such an arrangement would also be possible in animals with a slow closure rate, like the pig, mouse and rat (II III). In addition, it is possible that, in the rat, the initial inactive period of ductal closure coincides with a persisting right-to-left shunt (III). On the other hand, if a high arterial oxygen saturation were to be the cause of ductal closure also in animals in which it takes place almost instantaneously—as observed in the guinea-pig and rabbit—the onset of effective respiration within a few seconds of birth has to be demonstrated.

The experimentally induced delay in closure of the ductus arteriosus in hypothermic and hypoxic rats might be the basis for a brief discussion of the role of catecholamines (II VI). After oxygen, catecholamines are the most discussed cause of ductal closure (10 47 79). No definite conclusions concerning their effect can be drawn from the present investigations. It can nevertheless be surmised that acidosis (18) develops in hypothermic rats (II). Acidosis has also been demonstrated in newborn rats supplied with low oxygen concentration (85) as used in Paper VI. As adrenergic receptors are known to be hindered by lowering of the pH (14) the demonstrated delay in closure rate under hypothermia and hypoxia may indicate a possible role of catecholamines in ductal closure. However observations *in vivo* (10) and *in vitro* (47) indicate that variations in pH have no effect on closure of the ductus arteriosus. On the other hand, it may also be suggested that hypothermic rats are hypoxic (18). The observed delay in closure rate during hypothermia would then further support the importance of oxygen for ductal closure.

The delay in ductal closure rate observed in rats under hypothermia (II) does not support the suggestion that bradykinin might be of consequence for ductal closure (54 74). The formation of bradykinin is, in fact, stated to be activated by a decrease in temperature (54).

Clinical Interpretation

For morphological studies of the human ductus arteriosus, distension of the ductus prior to fixation (6) seems at present to be the most appropriate technique for its preservation. Using this technique, the ductal morphology in stillborn babies resembles that in newborn animals fixed by whole-body freezing (III). Similar morphological changes to those observed in the animals in the present study (II III) have been described in the human ductus during its closure (6). It can therefore be assumed that no essential differences do, in fact, exist between the ductal morphology and mode of ductal closure in the human being and in other mammals.

On the other hand, in view of possible over distension (55) distension fixation will fail to provide reliable data on inner diameter and wall thickness of the human ductus before closure, as well as during its physiological phase. The rate of ductal closure cannot therefore be established *in human* subjects as in animals (III). It is nevertheless tempting to ascertain the conceivable rate from results of clinical observations. Demonstration of a right-to-left shunt through the ductus *during the first hours of life* (2, 23, 58 75) *despite* a progressively falling pressure gradient (72, 75) indicates that no decrease in inner diameter occurs during this time. After the reverse shunt has been established, there is still a large flow through the ductus

in the human being (60) narrowing of the lumen in the human being and rat (4? 60) and prenatal closure of the lumen in the guinea pig (78) *Growth of the ductus prenatally* is in agreement with prevalent views of a large ductal blood flow throughout intrauterine life (11 50 81) Additional evidence is afforded by the finding that the ductus has more than half the cross-sectional area of the descending aorta in full term rats (IV)

The observation of a wide ductal lumen in newborns, and especially its dramatic decrease within minutes of birth in the guinea pig and *rabbit (III) clearly demonstrates that the phy*siological closure takes place shortly after birth (45) The prenatal ductal morphology in the guinea pig rabbit rat and mouse (IV) and the microradiographical observations in the rat and guinea pig (V) give no evidence of a prepara tory process in the media preceding the contrac tion (37 56) Nor is there any microradio-graphical support (V) for formation of exces-sive amounts of ground substance in the ductal wall *during closure* (42, 78) The extensive tissue lesions of the inner media observed in some species (III V) suggest that the ductus is not intended for repeated closure and opening, which has been reported to occur prenatally (50) and has also been demonstrated post natally under experimental conditions (10 45 68) Disappearance of the ductal lumen in all five species as a consequence of central displace-ment of the intima during the contraction (II III) *demonstrates that already during the phy*siological phase of closure, a functional ana tomical closure is achieved During the ana tomical phase, there is probably merely a con solidation of the tissue

Rate of ductal closure

No earlier report of the ductal closure rate has been presented for any species, whereas the time for closure of the ductus is given in a number of species, in morphological studies based on disappearance of the ductal lumen (38 4? 43 45 65 80 84) as well as in physiological in vestigations (1 3 8 10 25 58, 73) determined from arrest of the blood flow through the ductus.

The present studies have clearly demonstrated that determination of the closure rate has per mitted characterization *of the ductal closure in* different species in a more appropriate way than merely by observing disappearance of the ductal lumen (II III) Knowledge of the species diffe rences as regards closure rate should be the basis for selection of appropriate species for studies of experimental factors which might in-terfere with ductal closure. The validity of this concept is borne out by the experiments in the guinea pig when oxygen and nitrogen were supplied, and interruption of the umbilical cir culation was performed immediately on deli very and the effects had to be registered within the next few minutes (VI) In a similar experi ment in the guinea pig (67) the reduction in oxygen concentration was applied only after 3 minutes—*i.e.* after the period of most active constriction of the ductus—and the results were not recorded until 24 hours later In species with slow ductal closure, as in the rat a signi ficant response to hypothermia (II) and hy poxia (VI) could also be demonstrated by de-termining the closure rate.

The ductus arteriosus can however be as-sumed to close functionally before disappearance of its lumen (II) Already on reduction of the inner diameter to 20 per cent—occurring in the *guinea pig and* rabbit within ? minutes, in the mouse before the age of 30 minutes, in the rat within 1 hour and in the pig about 2 hours after birth—the corresponding ductal flow is namely decreased to less than 0 ? per cent at a constant pressure gradient. It is unlikely that changes in the pressure gradient will restore any consider *able flow since the flow through a* vessel is pro-portional to the fourth power of its radius, but directly proportional to the pressure gradient (35) Because of lack of knowledge of the ductal lumen in new borns, patency has therefore been ascribed to ductuses exhibiting only a minimal lumen (65 88)

Cause of ductal closure

Of factors which have proved to induce constriction of the ductus (9 10, 24, 45, 46, 47 79) only oxygen and certain vasoactive agents might be relevant in discussing causes of the physiological ductal closure.

The present results (VI) confirm that oxygen causes ductal closure in the guinea-pig (45) Furthermore, the observed delayed closure rate in rats under hypoxia supports the role of oxygen in ductal closure (VI) The mechanism of oxygen action is not, however satisfactorily explained. Its effect has been suggested to be mediated by a rise in the oxygen saturation of the blood perfusing the ductus (3 10, 46, 57 68) This implies that a reverse shunt through the ductus is initially established, a condition which has been demonstrated in the lamb (20) calf and foal (1) Such an arrangement would also be possible in animals with a slow closure rate, like the pig, mouse and rat (II, III) In addition, it is possible that, in the rat, the initial inactive period of ductal closure coincides with a persisting right-to-left shunt (III) On the other hand, if high arterial oxygen saturation were to be the cause of ductal closure also in animals in which it takes place almost instantaneously—as observed in the guinea-pig and rabbit—the onset of effective respiration within few seconds of birth has to be demonstrated.

The experimentally induced delay in closure of the ductus arteriosus in hypothermic and hypoxic rats might be the basis for a brief discussion of the role of catecholamines (II, VI) After oxygen, catecholamines are the most discussed cause of ductal closure (10, 47 79) No definite conclusions concerning their effect can be drawn from the present investigations. It can nevertheless be surmised that acidosis (18) develops in hypothermic rats (II) Acidosis has also been demonstrated in newborn rats supplied with low oxygen concentration (85) as used in Paper VI As adrenergic receptors are known to be hindered by lowering of the pH (14) the demonstrated delay in closure rate under hypothermia and hypoxia may indicate possible role of catecholamines in ductal closure How ever observations in vivo (10) and in vitro (47) indicate that variations in pH have no effect on closure of the ductus arteriosus. On the other hand, it may also be suggested that hypothermic rats are hypoxic (18) The observed delay in closure rate during hypothermia would then further support the importance of oxygen for ductal closure.

The delay in ductal closure rate observed in rats under hypothermia (II) does not support the suggestion that bradykinin might be of consequence for ductal closure (54 74) The formation of bradykinin is, in fact, stated to be activated by a decrease in temperature (54)

Clinical interpretation

For morphological studies of the human ductus arteriosus, distension of the ductus prior to fixation (6) seems at present to be the most appropriate technique for its preservation. Using this technique, the ductal morphology in stillborn babies resembles that in newborn animals fixed by whole-body freezing (III) Similar morphological changes to those observed in the animals in the present study (II III) have been described in the human ductus during its closure (6) It can therefore be assumed that no essential differences do, in fact, exist between the ductal morphology and mode of ductal closure in the human being and in other mammals.

On the other hand, in view of possible over distension (55) distension fixation will fail to provide reliable data on inner diameter and wall thickness of the human ductus before closure, as well as during its physiological phase The rate of ductal closure cannot therefore be established in human subjects as in animals (III) It is nevertheless tempting to ascertain the conceivable rate from results of clinical observations. Demonstration of a right to-left shunt through the ductus during the first hours of life (2, 23 38, 75) despite a progressively falling pressure gradient (72, 75) indicates that no decrease in inner diameter occurs during this time. After the reverse shunt has been established, there is still a large flow through the ductus

for some more hours (?) Demonstration of a measurable left-to-right shunt through the ductus only occasionally after the age of 15 hours (2 57 58 64 73) might however indicate that the ductus arteriosus at this time is severely narrowed and even closed in many cases. It therefore seems likely that the human ductus arteriosus will not constrict during an initial period with a persisting right-to-left shunt of approximately 3 hours, in contrast to all the species investigated in the present study

Dilatation of the human ductus arteriosus under hypoxia, and subsequent re-establishment of the constriction on recovery of the arterial oxygen saturation (44 57) make it likely that in human beings as well oxygen is the cause of ductal closure. Occasional observations of delayed closure in prematures, which have low arterial oxygen tension (5 19) further indicate the great importance of oxygen for closure of the ductus arteriosus. There is therefore reason to believe that the cause of ductal closure in human beings and other mammals is identical, although the mechanism is unknown.

As a conclusion, it seems justified to investigate the closure process in animals with respect to prenatal changes in the ductal morphology and postnatal interference with causes of ductal closure, in order to disclose the development of patent ductus arteriosus in human beings.

SUMMARY

In the present studies on closure of the ductus arteriosus in the pig, guinea-pig, rabbit, rat, and mouse, whole-body freezing was used for sacrifice and fixation. With this technique, the ductus is available for morphological studies in a state which can be considered to reflect its state in vivo. Examinations of its structure, as well as measurements of inner diameter and wall thickness, are therefore of consequence. The results presented confirm that the technique is valid for animals of different size, at least up to the size of a new-born pig.

In newborns of all species, the ductus arteriosus exhibits a rounded lumen with a smooth inner surface and a thin wall composed mainly of the media, which has straight elastic lamellas and slender interposed muscle cells. Observations of a progressive growth of the ductus during late intrauterine life indicate that its closure is initiated after birth. During closure, the ductus of all species displays similar morphological changes, which conclusively indicate that the narrowing is brought about by contraction of its muscle coat. Remodelling of the inner media enables an extensive contraction, and disappearance of the lumen is achieved already during the physiological phase of closure by central displacement of intimal cells.

Species differences exist in the ductal closure rate. The guinea-pig and rabbit exhibit a rapid closure rate of the ductus arteriosus, with a severe narrowing of its lumen already within 2 minutes. Newborns of the mouse and rat, on the other hand, display the same degree of ductal closure only after 30 minutes and 1 hour, respectively. In the pig a corresponding narrowing of the lumen is found only after 2 hours. Complete occlusion of the ductus follows in the guinea-pig and rabbit about 30 minutes after birth, while in the mouse disappearance of the lumen is observed only after 2 hours, in the rat after 3 hours and in the pig after 8 hours.—Information on the ductal closure rate is important for the planning of studies of factors which might interfere with closure.

Additional support has been obtained that oxygen is essential for closure of the ductus arteriosus. The proposed action of oxygen as mediated to the ductal wall by perfusing blood with high oxygen saturation, might be possible in animals with a slow closure rate like the pig, rat and mouse. On the other hand, if this is to apply in animals with an almost instantaneous closure rate—like the guinea pig and rabbit—the onset of effective respiration within a few seconds of birth has to be demonstrated. No definite conclusions can be drawn regarding the effect of catecholamines. Possible acidosis under conditions accompanied by delayed ductal closure rate might, however, indicate that adrenergic receptors are involved in the closure process, while on the other hand no support is obtained for ductal closure caused by bradykinin.

Comparisons between the results of the present investigations in animals, using whole-body freezing, and of an earlier reported study in human beings, using distension fixation, indicate that no essential differences do, in fact, exist in ductal morphology and mode of ductal closure between the human being and other mammals. Reported estimations of the blood flow through the ductus arteriosus in babies are, however, consistent only with a considerably lower ductal closure rate in human subjects than that observed in the investigated species. The concept of oxygen as an important factor for ductal closure in human beings is supported by the results of the present experiments in animals.

ACKNOWLEDGEMENTS

My sincere thanks are due to

Professor John Lind, Head of the Department of Paediatrics, Karolinska Institutet, for introducing me into the field of neonatal physiology. His personal interest in my work and his extensive knowledge in this field have been of the utmost value.

Professor Ture Petrén, former Head of the Department of Anatomy, Karolinska Institutet, who taught me gross anatomy, for his interest in my work.

Associate Professor K. Sune Larsson, responsible for the Swedish Medical Research Council's Teratology Research Unit, Karolinska Institutet, for his never failing interest in the problems arising during this study, for fruitful discussions and valuable help during the course of the investigations. His optimistic and enthusiastic attitude has been an unceasing source of inspiration. I wish to offer him my warm thanks for giving me the privilege of being a member of his research group.

Associate Professors Allan Beaudoin, Department of Anatomy, University of Michigan, Harry Boström, Medical Department III, St. Erik's Hospital, Karolinska Institutet, and Lars Gyllensten, Department of Histology, Karolinska Institutet, for critical reading of the manuscripts.

Associate Professor Ulf Friberg, Department of Histology, Karolinska Institutet, for stimulating collaboration in one investigation and valuable discussions of others.

Associate Professor Rune Cederlöf, Department of Environmental Hygiene, National Institute of Public Health, Stockholm, for advice on statistical methods.

Drs Margareta Eriksson and Lars Marsk and other colleagues for stimulating discussions and technical assistance.

Professor Chester A. Swinyard, representing the Association for the Aid of Crippled Children, New York, for his personal engagement in this project.

Mrs Ann Britt Dahlberg, Miss Solveig Johansson, Mrs Tollie Palm and Mrs Marie Louise Wadström for typing the manuscripts.

Mrs Margareta Edmark, Mrs Aino Hallberg, Mr Ove Helistrand, Mrs Anne Marie Johansson, Mrs Marianne Kjellberg, Mrs Git Lundin, Miss Eva Löfgren and Mr Rudolf Rudefjell for skilful technical assistance.

Mrs Erica Odelberg, for rapid and efficient revision of my English.

My wife, May, for her never-failing patience, encouragement and support throughout this work.

This investigation was supported by grants from

The Swedish Medical Research Council Nos 14X-993-02, 03 and 04 and 14P-993-02, 03 and 04 to the Teratology Research Unit, Karolinska Institutet, and

The Association for the Aid of Crippled Children, New York, as part of its international support for research on foetal growth and development.

Additional financial support has been received from

Expressens Fund for Prenatal Research, Stockholm.

Grants to Dr Ulf Friberg from the King Gustaf V 80th Birthday Fund and Knut and Alice Wallenberg Foundation.

REFERENCES

1 Amoroso, E. C., Dawes, G. S. & Mott, J. C. Patency of the ductus arteriosus in the newborn calf and foal. *Brit Heart J* 20 92, 1958.

2 Arcilla, R. A., Oh, W., Wallgren, G., *Hanson, J. S.*, Gessner, I. H. & Lind, J. Quantitative studies of the human neonatal circulation. II. Hemodynamic findings in early and late clamping of the umbilical cord. *Acta Paediat Scand* Suppl. 179 23, 1967

3. Assali, N. S., Morris, J. A., Smith, R. W. & Manson, W. A. Studies on ductus arteriosus circulation. *Circ Res* 13 478, 1963

4 Assali, N. S., Sehgal, N. & Marable, S. Pulmonary and ductus arteriosus circulation in the fetal lamb before and after birth. *Amer J Physiol* 202 536, 1962.

5 Auld, P. A. M. Delayed closure of the ductus arteriosus. *J Pediat*, 69 61 1966.

6 Bakker, P. M. *Morfogenese en Involutie van de Ductus Arteriosus bij de Mens.* (Thesis) Mouton & Co Den Haag 1962

7 Ballance, C. A. & Edmunds, W. *Ligation of the Great Arteries in Continuity.* McMillan and Co London 1891

8 Barclay, A. E., Franklin, K. J. & Prichard, M. M. L. *The Foetal Circulation.* Blackwell Scientific Publications, Ltd., Oxford 1944

9 Barcroft, J., Kennedy, J. A. & Mason, M. F. The relation of the vagus nerve to the ductus arteriosus in the guinea-pig. *J Physiol (London)* 92 1 P 1938.

10 Born, G. V. R., Dawes, G. S., Mott, J. C. & Renwick, B. R. The constriction of the ductus arteriosus caused by oxygen and by asphyxia in newborn lambs. *J Physiol (London)* 132 304 1956

11 Born, G. V. R., Dawes, G. S., Mott, J. C. & Widdicombe, J. G. Changes in the heart and lungs at birth. *Cold Spring Harb Symp Quant Biol*, 19 102, 1954

12 Boyd, J. D. The nerve supply of the mammalian ductus arteriosus. *J Anat* 75 457 1940.

13 Bunce, D. F. M. Structural differences between distended and collapsed arteries. *Angiology* 16 53 1965.

14 Bygdeman, S. Vascular reactivity in cats during induced changes in the acid-base balance of the blood. *Acta Physiol Scand* Suppl. 222, 1963.

15. Cassens, R. L., van Wagner, B. M. & Rushmer, R. F. Architecture of small arteries during vasoconstriction. *Circ Res* 10 666, 1962.

16. Condorelli, S. & Ungari, C. The period of functional closure of the foramen ovale and the ductus Botalli in the human newborn. *Cardiologia (Basel)* 36 274 1960.

17 Conn, H. J., Darrow, M. A. & Emmel, V. M. *Staining Procedures.* The Williams & Wilkins Co., Baltimore, Md. 1960, 2nd edition.

18. Cooper, K. E. Temperature regulation and its disorders, in D. V. Baron, N. Compston and A. M. Dawson (ed.) *Recent Advances in Medicine.* J. & A. Churchill Ltd, London 1968, p. 333

19 Danilowicz, D., Rudolph, A. M. & Hoffman, J. I. E. Delayed closure of the ductus arteriosus in premature infants. *Pediatrics* 37 74 1966.

20. Dawes, G. S., Mott, J. C. & Widdicombe, J. G. The cardiac murmur from the patent ductus arteriosus in newborn lambs. *J Physiol (London)* 128 344 1955

21 — The patency of the ductus arteriosus in newborn lambs and its physiological consequences. *J Physiol (London)* 128 361 1955.

22. Ekström, G. The surgical treatment of patent ductus arteriosus. *Acta Chir Scand* Suppl. 169 1952.

23 Eldridge, F. L., Hultgren, H. N. & Wigmore, M. E. The physiologic closure of the ductus arteriosus in the newborn infant. *J Clin Invest* 34 987 1955.

24 Eltherington, L., Hughes, T., Stoff, J. & Melmon, K. L. Unpublished observations. Cited by Melmon, K. L. and Cline, M. J.

25. Everett, N. B. & Johnson, R. J. A physiological and anatomical study of the closure of the ductus arteriosus in the dog. *Anat Rec* 110 103 1951

26. Fairfield, J. Effects of cold on infant rats. Body temperatures, oxygen consumption, electrocardiograms. *Amer J Physiol* 155 355 1948.

27 Gérard, G., De l'oblitération du canal artériel. Les théories et les faits. *J Anat (Paris)* 36 323 1900.

28. Gräper L. Die anatomischen Veränderungen kurz nach der Geburt. III. Ductus Botalli. *Z Anat Entwicklungsgesch 61* 312 1921
29 *Handbook / Biological Data.* W S. Spector (ed.) W B. Saunders Co., Philadelphia/London 1956
30. *Handbook of Chem stry and Phys cs.* The Chemical Rubber Co. Cleveland, Ohio 1964—65 45th edition.
31 Hanson, J S., Arcilla, R. A. Oh W., Wallgren G & Lind, J Quantitative studies of the human neonatal circulation. I Dye dilution. Principles and techniques. *Acta Paediat Scand* Suppl. *179* 7 1967
32 Hanna M T & Herbertson, J E. Concerning the postnatal obliteration of the umbilical vein and arteries the vitell ne vein and artery and the ductus arteriosus in the guinea pig. *Trans Kansas Acad S 41* 369 *1938.*
33. Harms, D Über den Bau und Verschluss des Ductus Arteriosus Botalli des Rindes. *Z Zellfo sch 72* 34 1966.
34 Hayek, H. von Der funktionelle Bau der Nabelarterien und des Ductus Botalli. *Z Anat Ent wickl ngsgesch 105* 15 1935
35 Haynes, R. H & Rodbard, S. Art rial and arteriolar systems Biophysical principles and physiology a D I Abramson (ed) *Blood Vessels and Lymphatics* Academic Press, New York 196 p 26
36. Hellström, B. & Nergårdh, A. The effect of high oxygen concentrations and hypothermia on the lung of the newborn mouse *Acta Paediat Scand 54* 457 1965
37 Hoffman, E. Die Obliteration des Ductus ar t riosus Botalli. *Langenbeck A k Klin Ch r 306* 289 1964
38 Horváth, L. & Szabó J Beiträge zum Problem der Struktur und des Verschlusses des Ductus Botall *Deutsch Z Ges G richtl Med 33* 175 1940.
39 House E. W & Ederstrom H E. Anatomical changes with age in the heart and ductus r teriosus n the dog after birth. *Anat Rec 160* 289 1968.
40 Hughes, T The aorticopulmonary rt ry of th cat — its location and postnatal closure. *Anat Rec 158* 491 1967
41 Hutschenreiter W On the beha iour of the ductus Botall of new-born rats following the pplication f amino-acetonitrile. *A t Biol M d German 14* 534 1965.
42. Ingen, H C. an *Morfologische Aspect van h t Sluitingsproc s va de Ductus A t riosus* (Thesis) Luctor t Emergo" Leiden 1964
43 Jager B. V & Wollenman, O J J An anatomical study of the closure of the ductus arteriosus. *Am J Path 18* 595 1942.
44 James, L. S. & Rowe, R. D The pattern of response of pulmonary and systemic arterial pressures n newborn and older infants to short periods of hypoxia. *J Pediat 51* 5 1967
45 Kennedy J A. & Clark, S. L., Observations on the ductus arteriosus of the guinea pig in relation to its method of closure. *Anat Rec 79* 349 1941
46. — Observations on the physiological reactions of the ductus arteriosus. *Amer J Physol 136* 140, *1942.*
47 Kovalčik V The response of the isolated ductus arteriosus to oxygen and anoxia. *J Physiol (London) 169* 185 *1963*
48. Langer C. Zur Anatomie der fötalen Kreislaufsorgane. *Z Gesell Aertze 13* 328, 1857
49 Larsson K. S. Studies on the closure of the secondary palate. III Autoradiographic and histochemical studies in the normal mouse embryo. *Acta M ph V erl Scand 4* 349 196..
50. Lind, J Stern, L. & Wegelius, C. *H man Foetal and Neonatal C culation.* Charles C. Thomas, Publisher Springfield, Ill. 1964
51 Linzenmeier G Der Verschluss des Ductus arteriosus Botalli nach der Geburt des Kindes. *Z G burt h Gynaek 76* 217 1914—15.
52. MacWilliam J A. On the properties of the arterial and venous walls. *Proc Roy Soc 70* 109 1902
53 Melka J Beitrag zur Kenntnis der Morphologie und Obliteration des Ductus arteriosus Botalli. *Anat Anz 61* 348 1926.
54 Melmon, K. L. & Cline, M. J Kinins. *Amer J Med* 43 153 1967
55. Mey W W Die Lebenswandlungen der Strukt von Arterien und Venen. *Verh Deutsch Ges K eislaufforsch 24* 15 1958.
56. Meye W W & Simon, E. Die präparatorische Angiomalacie des Ductus arteriosus Botalli als Voraussetzung seiner Engstellung und als Vorbild krankhafter Arterien eränderungen. *V chow A h Path 1 at 333* 119 1960.
57 Moss, A. J Emmanouilides, G C Adams, F H. & Chuang K. Response of ductus arteriosus and pulmonary and ystemic arterial pressure to changes in oxygen en ironment n newborn infants. *P diatric 33* 937 1964
58 Moss, A. J Emmanouilides, G & Duffie E R. Closure of the ductus arteriosus in the newborn infant. *Pediatrics 32* 25 1963
59 Noback, G J & Rehman, I The duct teriosus in the human fetus and newborn infant. *A t Re 81* 505 1941

60. Oldé, E. *De Ductus Arteriosus.* (Thesis) A. W. Sijthoff Uitgeversmaatschappij N. V. Leiden 1951

61. Ostle, B. *Statistic in Research.* The Iowa State College Press, Ames, Iowa 1954

62. Patten, B. M. *Human Embryology.* McGraw-Hill Book Co., New York 1968, 3rd edition.

63. Poland, P. E. & Campbell, M. Factors in the causation of persistent ductus arteriosus. (an *Hum Genet 24* 343, 1960.

64. Prec, K. J & Cassels, D. E. Dye dilution curves and cardiac output in newborn infants. Circulation, *11* 789 1965.

65. Record, R G & McKeown, T Anatomical closure of the ductus arteriosus in the guinea pig. *Clin Sci, 14* 213 1955.

66. — The effect of reduced atmospheric pressure on closure of the ductus arteriosus in the guinea pig *Clin Sci 14* 225, 1955.

67. — The effect of oxygen deficiency on closure of the ductus arteriosus in the newborn guinea pig *Clin Sci, 14* 711 1955

68. Rem, R L & Anderson, R P Constriction of the ductus arteriosus. Experimental observations in the newborn lamb. *J Surg Res, 4* 356, 1964

69. Reynolds, S R. M. The proportion of Wharton jelly in the umbilical cord in relation to distention of the umbilical arteries and vein, with observations on the folds of Hoboken *Anat R 113* 365 1952

70. — Hemodynamic characteristics of the fetal circulation *Amer J Obstet Gynec 68* 69 1954

71. Roeder H Die Histogenese des arteriellen Ganges Ein Beitrag zur Entwicklungsmechanik der Fötalwege *Arch Kinderheilk,* 33 147 1902

72. Rowe, R D & James, L S. The normal pulmonary arterial pressure during the first year of life *J P diat 51* 1 1957

73. Rudolph, A M Drorbaugh, J E., Auld, P A M Rudolph, A J Nadas, A S Smith, C. A. & Hubbel, J P Studies on the circulation in the neonatal period. The circulation in the respiratory distress syndrome *P diatrics 27* 551 1961

74. Rudolph, A M & Heymann, M. A. The fetal circulation *A Rev M d 19* 195 1968.

75. Saling, E. Neue U tersuchungsergebnisse über den Kreislauf des Kindes unmittelbar nach der Geburt. *Arch Gynaek 194:*287 1960.

76. Schaeffer J P. The behavior of elastic tissue in the postfetal occlusion and obliteration of the ductus arteriosus (Botalli) in *Sus Scrofa. J Exp Med, 19*: 129 1914.

77. Schanz, F.: Ueber den mechanischen Verschluss des Ductus arteriosus. *Arch Ges Physiol, 44* 239 1889

78. Sciacca, A. & Condorelli, M. Involution of the ductus arteriosus. A morphological and experimental study with critical review of the literature *Bibl Cardiol, Fasc 10* 1960.

79. Smith, R. W Morris, J A. & Assali, N. S. Effects of chemical mediators on the pulmonary and ductus arteriosus circulation in the fetal lamb. *Amer J Obstet Gynec 89* 252 1964

80. Sorretti F Analogie di struttura di meccanismo di obliterazione tr canale arterioso ed arterie ombelicali nei mammiferi. *Riv Biol, 44* 95, 1952.

81. Stahlman, M. Perinatal irculation. *P diat Clin N Amer 13* 753 1966

82. Strang, L B. The pulmonary circulation in the respiratory distress syndrome. *P diat Cli N Amer 13* 693, 1966.

83. Strassman, P Anatomische und physiologische Untersuchungen über den *Blutkreislauf* beim Neugeborenen. *Arch Gynaek, 45* 393, 1894

84. Swensson, A Beitrag zur Kenntnis on dem histologischen Bau und dem postembryonalen Verschluss des Ductus arteriosus Botalli. *Z M kr Anat F sch 46* 275, 1939

85. Thalme B Electrolyte and acid-base balance in fetal and maternal blood. An experimental and linical study *Acta Obstet Gynec S and 45* Suppl 8 1967

86. Variot, G. & Cailliau, F Recherches sur le processus d'oblitération du canal artériel. *Bull Soc Méd Hôp Paris 44* 1598, 1920.

87. Virchow R. Die Thrombosen der Neugeborenen, in *Gesammelt Abhandlu ge zu Wissenschaft lichen M dici* Meidinger Sohn & Co., Frankfurt A. M. 1856, p. 591

88. Wilcox, B. R., Roberts W C. & Carney E. K. The effect of reduced atmospheric oxygen concentration on closur of the ductus arteriosus in the dog. *J Surg Res,* 312, 1962.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 189 1969

ON THE ENDOGENOUS FORMATION OF CARBON MONOXIDE IN FULL-TERM NEWBORN INFANTS

BY S. P FÄLLSTRÖM

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden, without charge)

131. Mellbin, Tore, The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw. kr 25.— 1962
132. Bärjesson, Mats, Overweight Children. Sw. kr 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951 with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw. kr 25.— 1962
134. Möller, Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet*, June 30, 1962. Sw. kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr 25.— 1962
137. Hansen, A. E., Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr 25.— 1962
138. Wallgren, Eric Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus. Pre- and Postoperative Studies of Thirty-four Cases. Sw. kr 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller, James A., Jr and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress*. Copenhagen, 1961. Edited by K. Winge Flensborg. Sw. kr 30.— 1963
141. Wass-Höckert, Ole and Donner, Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study. Sw. kr 25.— 1963
142. Sterner, Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw. kr 25.— 1963
144. Sterky, Göran, Diabetic Schoolchildren. Sw. kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963*. Sw. kr 25.— 1963
147. Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw. kr 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children. Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr 20.— 1963
149. Valman, Three, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw. kr 25.— 1963
150. Mee, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics*. Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr 25.— 1964
154. Hall, Bertil, Mongolism on Newborns. A Clinical and Cytogenetic Study. Sw. kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Ch[illegible] from Attack to Symptom-free Status. Sw. kr 25.—
156. [illegible] ... and his Textbook on Paediatrics. Lib[illegible] Arvid Wallgren. Sw. kr 25.— 1964
157. [illegible] and Ockerman, P. A., Glycogenosis Type [illegible] Phosphatase) in Four Siblings. Sw. kr [illegible]
158. Aurelius, Dagfinn, C[illegible] in the Newborn Infant. Sw. kr 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress*, Stockholm, 1964. Edited by Y. Larsson. Sw. kr 15.— 1965
160. Ockerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr 25.— 1965
161. Petersson, T[illegible] and Ilkhvanen, L[illegible] Experimental Studies on Fetal and Neonatal Circulation. Sw. kr [illegible] 1965
162. Lundmark, Karl Martin, Bone Marrow [illegible] Proliferation in the [illegible] and in Haematological Diseases during Childhood. Sw. kr 25.— 1966
163. *Newborn Infant Care*, Edited by John Lind. Sw. kr 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live P[illegible] Sw. kr 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Maes, J. H., Bronchiectasis. A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr 25.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr 30.— 1966
168. Trolsberg, W. Focal Epileptic Discharges in Children, a Longitudinal Study. Sw. kr 25.— 1966
169. Dahl, Marit, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr 20.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr 20.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A Morphological and Bacteriological study based on 264 autopsies. Sw. kr 20.— 1966
172. *Festschrift in Memory of Constantin Chaccanis*. Sw. kr 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr 15.— 1967
174. Pettersson, Per Olov, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr 25.— 1967
175. Hanhart, Pentti, Vectorcardiographic Studies in the Newborn Infant. Sw. kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr 20.— 1967
177. *Proceedings of the Fifteenth Northern Paediatric Congress*, Bergen, 1967. Sw. kr 35.— 1967
178. Kjellberg, [illegible] Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation*. Edited by Göran Wallgren. Sw. kr 25.— 1967
180. Andersson, Hans Jürgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection. Using a Passive Haemagglutination Technique. Sw. kr 20.— 1966
181. Koch, Gösta, Lung Function and Acid Base Balance in the Newborn Infant. Sw. kr 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr 25.— 1968
183. Robertson, Ake, Fogel and Aperlow, Howard, A[illegible] ... of Human Placental Lipid Metabolism and Transport. Sw. kr 20.— 1968
184. Robertson, Bengt, The Intrapulmonary Arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr 25.— 1968
185. Andersson, Lars, Birth of Malformed Danish School Children in Relation to Height and Development and Social Conditions. Sw. kr 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr 20.— 1968
187. Karlberg, Petter, et al., The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr 27.— 1968
188. Mosesson, Gunnar W. and Ekstrand, Kerstin, Studies in Ulcerative Colitis in Infancy. A Clinical Study of 41 Cases and a Follow-up Study. Sw. kr 25.— 1968
189. Ekström, B. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969
190. Hedstad, P. Tore, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr 20.— 1969

Price Swed. kr 20.—

Cover printed by [illegible] by Almqvist & Wiksells Boktryckeri AB Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 189 1969

ON THE ENDOGENOUS FORMATION OF CARBON MONOXIDE IN FULL-TERM NEWBORN INFANTS

BY S. P FÄLLSTRÖM

ALMQVIST & WIKSELL STOCKHOLM

ACTA PÆDIATRICA SCANDINAVICA SUPPLEMENT 189 1969

FROM THE DEPARTMENTS OF PÆDIATRICS AND CLINICAL PHYSIOLOGY
UNIVERSITY OF GÖTEBORG, SWEDEN

On the endogenous formation of carbon monoxide in full term newborn infants

BY

S. P. FÄLLSTRÖM

GÖTEBORG 1968

This survey is based mainly on the following five communications, which will be referred to in the text by their Roman numerals, I–V

I Bjure, J and Fällström S P Endogenous formation of carbon monoxide in newborn infants. I Non-icteric and icteric infants without blood group incompatibility *Acta Paediat Scand 52* 361 1963

II Fällström, S P and Bjure, J Endogenous formation of carbon monoxide in newborn infants. II Rh haemolytic disease of the newborn. *Acta Paediat Scand 56* 365, 1967

III Fällström, S P and Bjure, J Endogenous formation of carbon monoxide in newborn infants III ABO incompatibility *Acta Paediat Scand 57* 137 1968

IV Fällström, S P Endogenous formation of carbon monoxide in newborn infants IV On the relation between the blood carboxyhaemoglobin concentration and the pulmonary elimination of carbon monoxide. *Acta Paediat Scand 57* 321 1968

V Fällström, S P Endogenous formation of carbon monoxide in newborn infants. V On the relation between the carboxyhaemoglobin concentration and the haemoglobin catabolism calculated from simultaneous determinations of carbon monoxide elimination and total haemoglobin. *Acta Paediat Scand 57* 487 1968.

Included in this survey are the results of determinations of the carbon monoxide (CO) content in room air from the Children s hospital and the Obstetric Department Sahlgren s Hospital, Göteborg, as well as the results of investigations into the methods used, which have not been presented earlier

A presentation in tabular form of the individual results can be obtained by request, from the author

Supported by grants from the Faculty of Medicine, University of Göteborg, the Majblomman Foundation and the Association for the Aid of Crippled Children

The statistical analyses were performed in cooperation with fil lic. Esbjörn Carlström and fil kand Bo Eriksson

The English text was revised by Roy Cooke M D

GÖTEBORG 1968
ELANDERS BOKTRYCKERI AKTIEBOLAG

CONTENTS

This survey is based mainly on the following five communications, which will be referred to in the text by their Roman numerals, I–V

I Bjure J and Fällström, S P Endogenous formation of carbon monoxide in newborn infants. I Non-icteric and icteric infants without blood group incompatibility *Acta Paediat Scand* 52 361 1963

II Fällström, S P and Bjure, J Endogenous formation of carbon monoxide in newborn infants. II Rh haemolytic disease of the newborn *Acta Paediat Scand* 56 365 1967

III Fällström, S P and Bjure, J Endogenous formation of carbon monoxide in newborn infants III ABO incompatibility *Acta Paediat Scand* 57 137 1968

IV Fällström S P Endogenous formation of carbon monoxide in newborn infants. IV On the relation between the blood carboxyhaemoglobin concentration and the pulmonary elimination of carbon monoxide. *Acta Paediat Scand* 57 321 1968

V Fällström, S P Endogenous formation of carbon monoxide in newborn infants. V On the relation between the carboxyhaemoglobin concentration and the haemoglobin catabolism calculated from simultaneous determinations of carbon monoxide elimination and total haemoglobin. *Acta Paediat Scand* 57 487 1968

Included in this survey are the results of determinations of the carbon monoxide (CO) content in room air from the Children s hospital and the Obstetric Department Sahlgren s Hospital, Göteborg, as well as the results of investigations into the methods used, which have not been presented earlier

A presentation in tabular form of the individual results can be obtained, by request, from the author

Supported by grants from the Faculty of Medicine, University of Göteborg, the Majblomman Foundation and the Association for the Aid of Crippled Children

The statistical analyses were performed in cooperation with fil lic. Esbjörn Carlström and fil kand. Bo Eriksson

The English text was revised by Roy Cooke, M D

GÖTEBORG 1968

CONTENTS

INTRODUCTION

At the end of the nineteenth century it was shown that the blood contains small amounts of a combustible gas [27], and it was soon found that this gas was probably carbon monoxide [47]. Since the gas was found in the blood in the absence of known exposure to CO the possibility of an endogenous production of CO was considered.

However it was not until the middle of this century that convincing proofs for an endogenous CO production were presented. In 1949 Sjöstrand reported the finding of increased levels of carboxyhaemoglobin (COHb)[1] in patients with haemolytic diseases [63]. The COHb was determined from the alveolar CO tension, which did not decrease after breathing CO-free air for several hours. Sjöstrand also demonstrated that the expired air always contains higher CO concentration than the inspired air and that this difference increases in haemolytic conditions [63, 64]. In a series of papers he showed that CO is formed during the degradation of haemoglobin in an amount corresponding to the formation of four molecules of CO for each molecule of haemoglobin [65, 66, 68]. This finding is in accordance with the theory for haemoglobin degradation, assuming oxidation of the α-methene carbon atom to carbon monoxide during the splitting of the porphyrin ring [26, 45]. During recent years Sjöstrand's results have been confirmed by Coburn and coworkers, using a technique virtually excluding the influence of exogenous CO [11–13].

Sjöstrand calculated that the amount of CO eliminated by the lungs in healthy adults is accounted for by the normal decay of circulating erythrocytes [65]. On the other hand Coburn *et al.* found in healthy adults as well as in patients with haemolytic diseases, that greater amounts of carbon monoxide were produced than could be explained on the basis of destruction of circulating erythrocytes alone [11–14]. Other investigations also indicate that additional sources for the endogenous CO production must be considered.

After the administration of ^{15}N- or ^{14}C glycine, labelled bilirubin rapidly appears in plasma and bile, and within a few days labelled stercobilin can be demonstrated in faeces [25, 42, 78]. After about 120 days there is a "late peak" of labelled stercobilin in faeces, corresponding to the destruction of aged red cells. The early labelled bilirubin which has been estimated to be 10–20 per cent of the total bilirubin production in normal man [25, 42] increases in situations with stimulated erythropoesis [2]. It has therefore been assumed to depend on the bone marrow activity and possible sources are haemoglobin or haemoglobin precursors in the marrow or circulating red cells with very short life span [52]. Part of this bilirubin is not associated with erythropoiesis but is probably derived from non-haemoglobin haemoproteins in the liver [78]. The formation of early labelled bilirubin is accompanied by CO formation [73, 74, 75], which thus constitutes a significant part of the endogenous CO production. Carbon monoxide is also formed during the degradation of myoglobin [67]. The myoglobin mass is however small compared with that of haemoglobin, and the turnover rate of its haeme is slow [70]. Its contribution to the endogenous CO production therefore can be assumed to be slight. From the available information it can be concluded that the endogenous CO production mainly depends on the degradation of haemoglobin, most of which is derived from circulating erythrocytes.

As mentioned above CO is continuously eliminated in the expired air. It has also been shown that oxidation of CO to CO_2 occurs *in vivo* [9, 43]. Luomanmäki estimated the mean

[1] In the following presentation COHb is expressed as CO saturation of the haemoglobin in per cent.

compensation would imply that CO elimination could be achieved at a constant CO tension gradient, irrespective of the total amount of haemoglobin.

Sjöstrand reported a positive correlation between the total amount of haemoglobin and the COHb level in healthy children and adults [63]. Hallberg could verify this finding in adult females but not in males [31]. Engstedt, calculating the rate of erythrocyte destruction from COHb, accounted for the total haemoglobin [18]. However available information does not permit a definite conclusion about the influence of the total haemoglobin *per se* on the COHb level.

Following Sjöstrands report on the finding of increased COHb levels in haemolytic diseases, several clinical investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions [14 18, 29 31 51]. Although the COHb level is only an indirect measure of the endogenous CO formation and theoretical objections can be raised against its use as an index of haemolysis, increased COHb levels have been found in the majority of patients with haemolytic disease compared with healthy adults. Furthermore, a significant correlation has been obtained between COHb and the rate of haemolysis as judged from red cell survival studies [14 18].

THE AIM OF THE PRESENT INVESTIGATION

Haemolytic diseases are frequent during the newborn period and an estimation of the degree of haemolysis is essential for their management. Furthermore, hyperbilirubinaemia is very common at this age in infants without demonstrable haemolytic disease. Information about the rate of haemoglobin catabolism is of great interest for the evaluation of the pathogenesis of the jaundice. Determination of the red cell survival is often not practicable in these infants and does not always give a true picture of the haemoglobin catabolism. An investigation of the endogenous CO formation therefore seemed to be an interesting approach to the problems of neonatal haemolytic disease and jaundice. Direct estimation of the endogenous CO production is technically difficult in small infants. Determination of the blood COHb level on the other hand can be done comparatively easily and is therefore applicable in clinical practice.

The main purpose of the present investigation was to evaluate the COHb level as an index of haemolysis during the newborn period. Part of the study was therefore devoted to some factors other than haemolysis known to influence the COHb level in blood.

The effect of exogenous CO on infants in the Children's hospital and in the Obstetric Department, Sahlgren's Hospital has been estimated from systematic determinations of the room air CO concentration.

The efficiency of the CO elimination in newborns was estimated from simultaneous determinations of the COHb level and the pulmonary CO elimination (IV).

The relation between COHb and the rate of haemolysis expressed as CO production per g haemoglobin was determined (V) and the influence of the venous haemoglobin concentration on this relation has been evaluated.

In order to establish the association between COHb and haemolysis in a clinical material the COHb level in Rh haemolytic disease, a clinically and serologically well-defined haemolytic process, was determined and related to the severity of the disease (II).

On the assumption that COHb reflects haemoglobin catabolism the COHb level was used to evaluate the contribution of increased bilirubin production to the jaundice in icteric newborns without blood group incompatibility (I, III).

In order to obtain information on the frequency of increased haemolysis in infants of ABO heterospecific pregnancies the COHb level was determined in infants with obvious

fractional oxidation rate in dogs to be 0 30 per cent of the body CO pool per hour and in two human males to 0 11 and 0 16 per cent per hour respectively [43]. These figures indicate that at physiological COHb levels oxidation of CO is of minor importance No other way to eliminate CO has been demonstrated [10] In a steady state the CO produced in the body is thus eliminated almost quantitatively in the expired air

The solubility coefficient of CO in water is extremely low [32] In the body CO therefore exists exclusively bound to haemoproteins, mainly to haemoglobin and myoglobin Each molecule of haemoglobin can bind four mole cules of CO corresponding to a CO capacity of 1 34 ml per g haemoglobin

There are two principle determinants of the COHb level in blood, the CO concentration in inspired air and the rate of formation and elimination of endogenous CO Blood COHb can be regarded as composed of one exogenous part (COHb) and one endogenous ($COHb_{end}$)

$$COHb = COHb_{ex} + COHb_{end} \quad (1)$$

Exogenous CO will influence the COHb level according to the Haldane equation

$$\frac{COHb}{O_2Hb} = M \times \frac{PI_{CO}}{Pc_{O_2}} \quad (2)$$

PI_{CO} = CO tension in inspired air in mm Hg
Pc_{O_2} = mean pulmonary capillary oxygen ten sion in mm Hg
O_2Hb = mean pulmonary capillary oxygen saturation in per cent
M = equilibrium constant with the nu merical value of 200–250

Several investigators have considered the effect of inspiring high CO concentrations on the COHb level in blood [53] but reports on the influence of CO concentrations in air in the normal range are sparse Coburn *et al* estimated that in hospital wards (Philadelphia) room air CO was responsible for 0 40 per cent COHb or about half the normal mean level [12] In non-smoking Navy divers (Bethesda) the COHb level decreased from 0 88±0 21 per cent to 0 75±0 11 per cent after breathing air with a low and *constant CO* concentration for several days [15] The influence of exogenous CO must vary considerably in *different situa*tions and may for instance in smokers, greatly surpass that of the endogenous CO production

If obvious exposure to CO is avoided, the COHb level will to a high degree be determined by the formation and elimination of endogenous CO After injection of haemoglobin or damaged erythrocytes the CO production and the alveolar CO concentration rapidly increase [13 68]. The COHb level can therefore be assumed to reflect an increased rate of haemolysis almost instantly There are reasons to believe that the elimination of CO is determined by the same factors that influence the CO transfer from alveolar air to pulmonary capillary blood The main factors influencing the gas transfer are assumed to be the alveolar ventilation, pulmonary blood flow haemoglobin concentra tion blood pressures in the pulmonary circula tion mean pulmonary capillary oxygen tension and the CO tension gradient [4 5 19]. Because of the time constant for the equilibrium a change in any of these variables of short duration will not alter the COHb level appreciably but their effect is mainly an expression of the mean levels for periods of several hours

Since the endogenous CO production depends mainly on the degradation of circulating haemoglobin it is related to the total amount of haemoglobin. Thus a large haemoglobin mass implies a large CO production, even at a normal rate of haemolysis The haemoglobin mass is correlated to the body size and variations in CO production depending on this factor should be compensated for by variations in respiratory minute volume and diffusing capacity The haemoglobin concentration the other determinant of the haemoglobin mass, also influences the gas transfer between blood and alveoli The pertinent question is to what extent the large CO production of a large haemoglobin mass is compensated for by a more efficient CO elimination An efficient

compensation would imply that CO elimination could be achieved at a constant CO tension gradient, irrespective of the total amount of haemoglobin.

Sjöstrand reported a positive correlation between the total amount of haemoglobin and the COHb level in healthy children and adults [63]. Hallberg could verify this finding in adult females but not in males [31]. Engstedt, calculating the rate of erythrocyte destruction from COHb, accounted for the total haemoglobin [18]. However available information does not permit a definite conclusion about the influence of the total haemoglobin *per se* on the COHb level.

Following Sjöstrands report on the finding of increased COHb levels in haemolytic diseases, several clinical investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions [14 18, 29 31 51]. Although the COHb level is only an indirect measure of the endogenous CO formation and theoretical objections can be raised against its use as an index of haemolysis, increased COHb levels have been found in the majority of patients with haemolytic disease compared with healthy adults. Furthermore, a significant correlation has been obtained between COHb and the rate of haemolysis as judged from red cell survival studies [14 18].

THE AIM OF THE PRESENT INVESTIGATION

Haemolytic diseases are frequent during the newborn period and an estimation of the degree of haemolysis is essential for their management. Furthermore, hyperbilirubinaemia is very common at this age in infants without demonstrable haemolytic disease. Information about the rate of haemoglobin catabolism is of great interest for the evaluation of the pathogenesis of the jaundice. Determination of the red cell survival is often not practicable in these infants and does not always give a true picture of the haemoglobin catabolism. An investigation of the endogenous CO formation therefore seemed to be an interesting approach to the problems of neonatal haemolytic disease and jaundice. Direct estimation of the endogenous CO production is technically difficult in small infants. Determination of the blood COHb level on the other hand can be done comparatively easily and is therefore applicable in clinical practice.

The main purpose of the present investigation was to evaluate the COHb level as an index of haemolysis during the newborn period. Part of the study was therefore devoted to some factors other than haemolysis known to influence the COHb level in blood.

The effect of exogenous CO on infants in the Children's hospital and in the Obstetric Department, Sahlgren's Hospital has been estimated from systematic determinations of the room air CO concentration.

The efficiency of the CO elimination in newborns was estimated from simultaneous determinations of the COHb level and the pulmonary CO elimination (IV).

The relation between COHb and the rate of haemolysis expressed as CO production per g haemoglobin was determined (V) and the influence of the venous haemoglobin concentration on this relation has been evaluated.

In order to establish the association between COHb and haemolysis in a clinical material the COHb level in Rh haemolytic disease, a clinically and serologically well-defined haemolytic process, was determined and related to the severity of the disease (II).

On the assumption that COHb reflects haemoglobin catabolism the COHb level was used to evaluate the contribution of increased bilirubin production to the jaundice in icteric newborns without blood group incompatibility (I, III).

In order to obtain information on the frequency of increased haemolysis in infants of ABO heterospecific pregnancies the COHb level was determined in infants with obvious

signs of haemolytic disease as well as in infants without apparent signs of increased haemolysis (III)

MATERIAL

The investigation was restricted to infants with a birth weight above 2500 g. In the majority of the infants the endogenous CO formation was estimated from the COHb level in blood and therefore these infants were selected in a way that the influence of other factors on the COHb level was reduced.

The following groups of newborn infants were studied

Group 1 Seventy-seven healthy newborns without jaundice at repeated examinations (II III) The bilirubin concentration, measured in 39 of the infants, was below 10 mg per 100 ml Blood group incompatibility between infant and mother was excluded One COHb value from each of 75 infants constitute the basis for calculation of normal mean values and standard deviations after birth. In twelve of the infants the COHb level in cord blood was also determined

The original normal material comprised 35 infants (I) Six of these infants were later excluded because of divinylether anaesthesia or instrumental delivery The material was supplemented with 33 infants from group no 5 together with 15 other infants without jaundice

Group 2. Fifty nine infants with Rh haemolytic disease (II)

Group 3 Sixty-two infants selected because of jaundice associated with ABO incompatibility (III) Rh isoimmunization was excluded in all cases

Group 4 Forty six infants of ABO heterospecific pregnancies selected without regard to the degree of bilirubinaemia (III)

Group 5 Sixty-one infants of ABO homospecific pregnancies also selected without regard to the degree of bilirubinaemia (III)

Group 6 Forty-six infants with jaundice but no blood group incompatibility or other signs of haemolytic disease (III) Twenty-nine of these infants were included in the first report (I).

All infants in group nos 1–6 fulfilled the foll ing criteria None of the mothers was smoker No COHb values from cord blood or from the first day of life were included if volat anaesthetics such as divinylether or trichlc ethylene had been given to the mothers during the delivery Infants delivered by means of Caesarean section or instrumental delivery were not included in the study A few mothers had preeclampsia but no other serious maternal diseases were present. Severe haemorrhage did not occur during the pregnancy or labour

In the majority of cases the mother received 10 mg and the infant 1 mg of vitamin K_1 None of the infants received more than 5 mg.

Signs of asphyxia were not present in the infants with three exceptions. One infant in group no 2 had slight extrauterine asphyxia and in two other infants of that group low fetal heart rate had been registered No infant with clinical signs of respiratory disease was investigated There were no signs of infection or cerebral damage Infants with cephalhaematomata, large cutaneous bruises, melena or other signs of haemorrhage were also excluded from the study No infants were studied after exchange transfusion All infants were in good condition at the time of investigation.

Group 7 Simultaneous determinations of the COHb level and the pulmonary CO elimination were performed on 43 infants (IV) These infants comprised 15 without blood group incompatibility 10 with ABO incompatibility (7 of these were included in group no 3) and 18 infants with Rh haemolytic disease

The infants, to a large extent fulfilled the above mentioned criteria However since the aim of this part of the study was to establish the relation between COHb and CO elimination, the origin of the CO pool was not of primary interest Therefore a few infants were included although their mothers were smokers and some infants were studied after exchange transfusion

In 32 of the infants the total amount of haemoglobin was also determined and the rate of haemolysis was calculated as CO production per g haemoglobin (V). In these infants the influence of exogenous CO was limited to that of the CO in the ambient air

METHODS

The endogenous CO metabolism can be studied in different ways. In a steady state the pulmonary CO elimination equals the endogenous CO formation which thus can be determined from the respiratory minute volume and the difference between the CO concentrations in inspired and expired air This method has been used by Wranne in newborn infants, but according to him its precision is not very high [76] Coburn *et al* have developed another procedure which allows the determination of the endogenous CO production independent of exogenous CO and variations in CO elimination by using a rebreathing system and measuring the increase per unit time of the CO saturation in blood and the CO capacity of the body [11]. For precise determination of the COHb increment rebreathing during two or more hours was necessary Both these methods require the use of breathing systems and are therefore not easily applicable for routine use in small infants.

Determination of the COHb level in blood offers another possibility to study the CO metabolism and under certain prerequisite conditions the COHb gives information about the endogenous CO formation. Sjöstrand opened a new field for haematological research, when he introduced the method for indirect determination of low COHb levels from the alveolar CO tension [61]. Since that time methods have been described allowing direct determination of small amounts of CO in blood with a high precision. They require only small amounts of blood and are thus suitable for use in infants.

Determination of the CO concentration in gas mixtures

The amount of CO in gas mixtures was determined with a Hopcalite Stalex CO-meter according to the method described by Linderholm and Sjöstrand [40]. The procedure used in the present investigation was practically identical with that reported originally

In the CO-meter CO is oxidized to CO_2 in the presence of the catalyst *Hopcalite* and the liberated heat is measured by thermistors incorporated in a Wheatstone's bridge. The output from the bridge is registered on a potentiometer writer Carbon monoxide introduced into the CO-free carrier gas causes a deflection on the potentiometer writer

If very low CO concentrations in air shall be measured a large gas sample (5–10 l) must be used and the carrier gas must be replaced by the unknown sample. After 5–10 minutes the deflection reaches a plateau, *i.e* the heat loss from the measuring cell equals the heat liberated during the combustion of CO At a constant flow rate through the CO-meter the height of the plateau is proportional to the CO concentration of the gas. The procedure allows the determination of CO concentrations as low as 0.1 part per million (ppm) [40]. High CO concentrations are analyzed by rapid injection of a small volume of the gas sample into the carrier gas. In this case a steady state between heat production and loss is never reached and the deflection takes the appearance of a spike. If the sample is introduced into the carrier gas in less than twenty seconds the height of the deflection is proportional to the amount of CO injected [40]. In this way 0 1 µl CO can be detected by the CO-meter [41].

The response of the Hopcalite CO-meter has been shown to be linear within a wide range of CO concentrations [31 40]. The linearity of the CO-meter used for the present investigations was checked and confirmed for the actual ranges. For the analysis of low CO concentrations in air the sample replaced

AB Stålex, Stockholm.

signs of haemolytic disease, as well as in infants without apparent signs of increased haemolysis (III)

MATERIAL

The investigation was restricted to infants with a birth weight above 2500 g. In the majority of the infants the endogenous CO formation was estimated from the COHb level in blood, and therefore these infants were selected in a way that the influence of other factors on the COHb level was reduced

The following groups of newborn infants were studied

Group 1 Seventy-seven healthy newborns without jaundice at repeated examinations (II III) The bilirubin concentration, measured in 39 of the infants, was below 10 mg per 100 ml Blood group incompatibility between infant and mother was excluded One COHb value from each of 75 infants constitute the basis for calculation of normal mean values and standard deviations after birth In twelve of the infants the COHb level in cord blood was also determined

The original normal material comprised 35 infants (I) Six of these infants were later excluded because of divinylether anaesthesia or instrumental delivery The material was supplemented with 33 infants from group no 5 together with 15 other infants without jaundice

Group 2 Fifty nine infants with Rh haemolytic disease (II)

Group 3 Sixty two infants selected because of jaundice associated with ABO incompatibility (III) Rh isoimmunization was excluded in all cases.

Group 4 Forty six infants of ABO heterospecific pregnancies selected without regard to the degree of bilirubinaemia (III)

Group 5 Sixty-one infants of ABO homospecific pregnancies also selected without regard to the degree of bilirubinaemia (III)

Group 6 Forty-six infants with jaundice but no blood group incompatibility or other signs of haemolytic disease (III). Twenty-nine of these infants were included in the first report (I).

All infants in group nos 1–6 fulfilled the following criteria None of the mothers was smoker No COHb values from cord blood or from the first day of life were included, if volatile anaesthetics such as divinylether or trichlor ethylene had been given to the mothers during the delivery Infants delivered by means of Caesarean section or instrumental delivery were not included in the study A few mothers had preeclampsia but no other serious maternal diseases were present. Severe haemorrhage did not occur during the pregnancy or labour

In the majority of cases the mother received 10 mg and the infant 1 mg of vitamin K_1 None of the infants received more than 5 mg.

Signs of asphyxia were not present in the infants with three exceptions. One infant in group no 2 had slight extrauterine asphyxia and in two other infants of that group low fetal heart rate had been registered No infant with clinical signs of respiratory disease was investigated There were no signs of infection or cerebral damage Infants with cephalhaematomata, large cutaneous bruises, melena or other signs of haemorrhage were also excluded from the study No infants were studied after exchange transfusion. All infants were in good condition at the time of investigation

Group 7 Simultaneous determinations of the COHb level and the pulmonary CO elimination were performed on 43 infants (IV) These infants comprised 15 without blood group incompatibility 10 with ABO incompatibility (7 of these were included in group no 3) and 18 infants with Rh haemolytic disease

The infants, to a large extent fulfilled the above mentioned criteria However since the aim of this part of the study was to establish the relation between COHb and CO elimination the origin of the CO pool was not of primary interest Therefore a few infants were included although their mothers were smokers and some infants were studied after exchange transfusion

In 31 of the infants the total amount of haemoglobin was also determined and the rate of haemolysis was calculated as CO production per g haemoglobin (V). In these infants the influence of exogenous CO was limited to that of the CO in the ambient air

METHODS

The endogenous CO metabolism can be studied in different ways. In a steady state the pulmonary CO elimination equals the endogenous CO formation, which thus can be determined from the respiratory minute volume and the difference between the CO concentrations in inspired and expired air. This method has been used by Wranne in newborn infants, but according to him its precision is not very high [76]. Coburn *et al.* have developed another procedure which allows the determination of the endogenous CO production independent of exogenous CO and variations in CO elimination by using a rebreathing system and measuring the increase per unit time of the CO saturation in blood and the CO capacity of the body [11]. For precise determination of the COHb increment rebreathing during two or more hours was necessary. Both these methods require the use of breathing systems and are therefore not easily applicable for routine use in small infants.

Determination of the COHb level in blood offers another possibility to study the CO metabolism and under certain prerequisite conditions the COHb gives information about the endogenous CO formation. Sjöstrand opened a new field for haematological research, when he introduced the method for indirect determination of low COHb levels from the alveolar CO tension [61]. Since that time methods have been described allowing direct determination of small amounts of CO in blood with a high precision. They require only small amounts of blood and are thus suitable for use in infants.

Determination of the CO concentration in gas mixtures

The amount of CO in gas mixtures was determined with a Hopcalite Stalex CO-meter[1] according to the method described by Linderholm and Sjöstrand [40]. The procedure used in the present investigation was practically identical with that reported originally

In the CO-meter CO is oxidized to CO_2 in the presence of the catalyst Hopcalite and the liberated heat is measured by thermistors incorporated in a Wheatstone's bridge. The output from the bridge is registered on a potentiometer writer. Carbon monoxide introduced into the CO-free carrier gas causes a deflection on the potentiometer writer

If very low CO concentrations in air shall be measured a large gas sample (5–10 l) must be used and the carrier gas must be replaced by the unknown sample. After 5–10 minutes the deflection reaches a plateau, i.e. the heat loss from the measuring cell equals the heat liberated during the combustion of CO. At a constant flow rate through the CO-meter the height of the plateau is proportional to the CO concentration of the gas. The procedure allows the determination of CO concentrations as low as 0.1 part per million (ppm) [40]. High CO concentrations are analyzed by rapid injection of a small volume of the gas sample into the carrier gas. In this case a steady state between heat production and loss is never reached and the deflection takes the appearance of a spike. If the sample is introduced into the carrier gas in less than twenty seconds the height of the deflection is proportional to the amount of CO injected [40]. In this way 0.1 µl CO can be detected by the CO-meter [41].

The response of the Hopcalite CO-meter has been shown to be linear within a wide range of CO concentrations [31, 40]. The linearity of the CO-meter used for the present investigations was checked and confirmed for the actual ranges. For the analysis of low CO concentrations in air the sample replaced

---

[1] AB Stålex, Stockholm.

the carrier gas for a period of three minutes This length of time was found to be convenient because of the good reproducibility of the deflections and the saving of time and sample gas The height of the 3 minutes deflection in per cent of the height of the plateau was found to be 83 0±5 4 in the range 0 4–1 5 ppm (n=7) and 81 3±4.2 in the range 2.0–2.5 ppm (n=10) The relation can thus be assumed to be constant in the actual range

The sensitivity of the CO-meter varies from time to time and therefore the sample always has to be compared with a calibrating gas analyzed immediately before or after the sample Calibrating gas[1] with approximately the same CO concentration as the sample was used The concentration of the calibrating gas was determined through repeated analyses against dilutions of "pure" CO in CO-free air as described by Bjure [4]. The CO concentration was checked regularily during the period of use and was found to be constant Each new calibrating gas was analyzed against the preceding one and against dilutions. Thus all calibrating gases were thoroughly matched against each other throughout the study

In the present investigation samples with CO concentration between 0 04 and 0 08 per cent (400–800 ppm) were analyzed with a random error of ±0 0005 per cent CO (±5 ppm) Low CO concentrations in the range 0 00005–0 00050 per cent (0 5–5 ppm) were determined with an error of ±0 000007 per cent CO (±0 07 ppm)

Determination of the COHb level in blood

The CO content in blood was determined according to Linderholm *et al* and their standard procedure was used [41] The CO was released from the haemoglobin by 10 per cent sulphuric acid in an extraction chamber and measured in the Hopcalite CO-meter The extraction chamber was carefully cleaned with 1 per cent NaOH and distilled water between the analyses Usually 2 ml of blood was used for the analysis The COHb level was calculated from the CO content and the haemoglobin concentration using 1 34 ml per g as the CO combining capacity of haemoglobin

The Hopcalite method is not quite specific for CO and other volatile combustible substances such as acetone, ethanol and ammonia may interfere with the CO analyses. Under normal conditions the amount of interfering gases in the blood is small The CO-meter is not able to demonstrate any combustible gas in normal plasma [59] The COHb values found with the Hopcalite method in non-smoking healthy adults agreed well with those reported with the infrared [22] or gaschromatographic method [15] Sjöstrand s statement that for practical purposes the Hopcalite method can be regarded as specific for CO [59], thus seems to be valid

There are no reasons to believe that this does not hold true for the newborn infant under physiological conditions It was found however that volatile anaesthetics such as divinylether given to the mother during the second stage of delivery were associated with the finding of large amounts of combustible gas in the cord blood (Fig. 1) Nitrous oxide also causes deflections on the potentiometer writer but does not seem to pass the placenta in appreciable amounts with the type of intermittent administration used here (1).

The random error of a COHb determination calculated from duplicate determinations was found to be ±0 047 per cent COHb in the range 0 4–1 0 per cent and ±0 049 per cent COHb in the range 1 0–4 0 per cent

The COHb levels in two equivalent groups of full term healthy newborns, aged 4 days and with bilirubin concentrations below 10 mg per 100 ml were determined during the years 1961–63 and 1964–66 respectively The COHb levels, 0 82±0 15 per cent (n=14) and 0 81±0 17 (n=16) agreed well indicating a good reproducibility of the method

---

[1] Manufactured by AGA Stockholm.

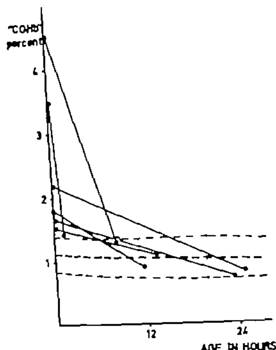


Fig. 1 Measured COHb level in cord blood and on the first day after birth in infants whose mothers received divinylether anaesthesia during the second stage of labour

Determination of the pulmonary CO elimination (IV)

An open circuit breathing system was used for the determination of the pulmonary CO elimination with the infant attached by means of a nose mask without valves. The infant breathed room air which was sucked through the mask at a constant flow rate and collected in bags. The CO elimination per unit time ($\dot{V}_{CO}$) was calculated from the increase of the CO concentration in the air sucked through the system and the volume of the passing air. The Hopcalite CO-meter was used for the CO analyses. Special precautions were necessary to prevent contamination of the collected air with exogenous CO or with other volatile substances combustible in the CO-meter.

Preliminary investigations showed a very low CO elimination when the room air CO concentration was high. This might depend on a non-steady state, since it was found that the CO elimination was reduced after an increase of the inspired CO concentration (Fig. 2). In order to reduce the effect of variations in inspired CO only investigations with room air CO below 1.5 ppm were included. During the period of study two infants were excluded for this reason. Furthermore, at the time of investigation the infant breathed air which had been collected during 30–60 min prior to the study from the ward.

Duplicate determinations of the CO elimination were done in most cases. The random error of a single determination was calculated from the difference between duplicate determinations to ±0.26 μl per min. Wranne estimated the CO elimination in small infants with practically the same error 0.27 μl per min using a different procedure for the collection of expired air and another CO-method [76].

Determination of the total amount of haemoglobin (V)

A modification of the open circuit CO-method [54] was used for the determination of total haemoglobin. The same breathing system and nose mask were used as for the determination of the CO elimination. The infant breathed a mixture of CO and air during a period of 10 min. The amount of CO absorbed by the infant was calculated from the volume of air passing through the system and the decrease of the

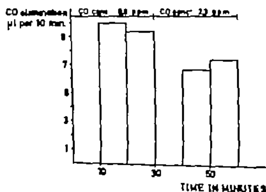


Fig. 2. Pulmonary CO elimination in one infant breathing air with 0.9 and then 2.3 ppm CO

the carrier gas for a period of three minutes This length of time was found to be convenient because of the good reproducibility of the deflections and the saving of time and sample gas The height of the 3 minutes deflection in per cent of the height of the plateau was found to be 83 0±5 4 in the range 0 4–1 5 ppm ($n=7$) and 81.3±4.2 in the range 2.0–2.5 ppm ($n=10$) The relation can thus be assumed to be constant in the actual range

The sensitivity of the CO-meter varies from time to time and therefore the sample always has to be compared with a calibrating gas analyzed immediately before or after the sample Calibrating gas[1] with approximately the same CO concentration as the sample was used The concentration of the calibrating gas was determined through repeated analyses against dilutions of "pure" CO in CO-free air as described by Bjure [4] The CO concentration was checked regularily during the period of use and was found to be constant Each new calibrating gas was analyzed against the preceding one and against dilutions Thus all calibrating gases were thoroughly matched against each other throughout the study

In the present investigation samples with CO concentration between 0 04 and 0 08 per cent (400–800 ppm) were analyzed with a random error of ±0 0005 per cent CO (±5 ppm) Low CO concentrations in the range 0 00005–0 00050 per cent (0 5–5 ppm) were determined with an error of ±0 000007 per cent CO (±0 07 ppm)

Determination of the COHb level in blood

The CO content in blood was determined according to Linderholm *et al* and their standard procedure was used [41] The CO was released from the haemoglobin by 10 per cent sulphuric acid in an extraction chamber and measured in the Hopcalite CO-meter The extraction chamber was carefully cleaned with 1 per cent NaOH and distilled water between the analyses Usually 2 ml of blood was used for the analysis The COHb level was calculated from the CO content and the haemoglobin concentration using 1 34 ml per g as the CO combining capacity of haemoglobin

The Hopcalite method is not quite specific for CO and other volatile combustible substances such as acetone, ethanol and ammonia may interfere with the CO analyses. Under normal conditions the amount of interfering gases in the blood is small The CO-meter is not able to demonstrate any combustible gas in normal plasma [59]. The COHb values found with the Hopcalite method in non-smoking healthy adults agreed well with those reported with the infrared [22] or gaschromatographic method [15]. Sjöstrand s statement that for practical purposes the Hopcalite method can be regarded as specific for CO [59] thus seems to be valid.

There are no reasons to believe that this does not hold true for the newborn infant under physiological conditions It was found, however that volatile anaesthetics such as divinylether given to the mother during the second stage of delivery were associated with the finding of large amounts of combustible gas in the cord blood (Fig 1) Nitrous oxide also causes deflections on the potentiometer writer but does not seem to pass the placenta in appreciable amounts with the type of intermittent administration used here (1).

The random error of a COHb determination calculated from duplicate determinations was found to be ±0 047 per cent COHb in the range 0 4–1 0 per cent and ±0 049 per cent COHb in the range 1 0–4 0 per cent

The COHb levels in two equivalent groups of full term healthy newborns, aged 4 days and with bilirubin concentrations below 10 mg per 100 ml were determined during the years 1961–63 and 1964–66 respectively The COHb levels, 0 82±0 15 per cent ($n=14$) and 0 81±0 17 ($n=16$) agreed well indicating a good reproducibility of the method.

---

[1] Manufactured by AGA, Stockholm.

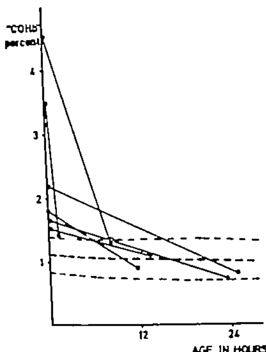


Fig. 1. Measured COHb level in cord blood and on the first day after birth in infants whose mothers received divinylether anaesthesia during the second stage of labour

Determination of the pulmonary CO elimination ($\dot{V}$)

An open circuit breathing system was used for the determination of the pulmonary CO elimination with the infant attached by means of a nose mask without valves. The infant breathed room air which was sucked through the mask at a constant flow rate and collected in bags. The CO elimination per unit time ($\dot{V}_{CO}$) was calculated from the increase of the CO concentration in the air sucked through the system and the volume of the passing air. The Hopcalite CO-meter was used for the CO analyses. Special precautions were necessary to prevent contamination of the collected air with exogenous CO or with other volatile substances combustible in the CO-meter.

Preliminary investigations showed a very low CO elimination when the room air CO concentration was high. This might depend on a non-steady state, since it was found that the CO elimination was reduced after an increase of the inspired CO concentration (Fig. 2). In order to reduce the effect of variations in inspired CO only investigations with room air CO below 1.5 ppm were included. During the period of study two infants were excluded for this reason. Furthermore, at the time of investigation the infant breathed air which had been collected during 30-60 min prior to the study from the ward.

Duplicate determinations of the CO elimination were done in most cases. The random error of a single determination was calculated from the difference between duplicate determinations to ±0..6 µl per min. Wranne estimated the CO elimination in small infants with practically the same error 0..7 µl per min, using a different procedure for the collection of expired air and another CO-method [76].

Determination of the total amount of haemoglobin (Hb)

A modification of the open circuit CO-method [54] was used for the determination of total haemoglobin. The same breathing system and nose mask were used as for the determination of the CO elimination. The infant breathed a mixture of CO and air during a period of 10 min. The amount of CO absorbed by the infant was calculated from the volume of air passing through the system and the decrease of the

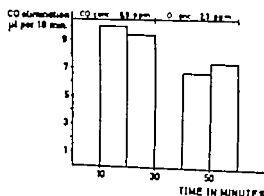


Fig. 2. Pulmonary CO elimination in one infant breathing air with 0.9 and then 2.3 ppm CO.

CO concentration in the gas mixture The COHb level in blood was measured *before and after* CO breathing. The total amount of haemoglobin was calculated from the increase of the CO saturation in blood and the amount of CO absorbed using 1 34 *ml* CO per g as the CO combining capacity of haemoglobin

The value 1.34 is obtained using 66 400 for the molecular weight of haemoglobin. However this has recently been calculated to be 64 458 [7] corresponding to a CO capacity of 1.39 ml per g haemoglobin. Since the haemoglobin method was standardized with haemoglobin solutions determined by their oxygen capacity the COHb values are not influenced by the value for the haemoglobin molecular weight. The total amount of haemoglobin determined by the CO-method would decrease 3.5 per cent if the factor 1.39 was used.

The distribution of CO in the body is determined by the amounts of different haemoproteins and their relative affinities for CO The main part of the CO is bound to circulating haemoglobin and equilibrium is reached rapidly in the blood [43] The extravascular CO pool mainly consists of CO bound to myoglobin The size of this pool has been estimated from simultaneous determinations of the blood volume by a CO dilution technique and by dilution of isotope labelled red cells to 16 ± 10 per cent in man [49] Equilibrium between intravascular and extravascular CO pools is reached within 15–45 min in dogs [43] Sjöstrand estimated that with his rebreathing CO method about 5 per cent of administered CO was bound to extravascular haemoproteins after 15 min rebreathing [62]. In the present procedure the extravascular CO loss was probably of less importance since the CO exposure was shorter and the initial alveolar CO tension lower than in the rebreathing method Furthermore the relative amount of myoglobin is smaller in newborns than in adults [33]

During the period of CO breathing the circulating erythrocytes can be assumed to pass the pulmonary capillaries several times, which should allow a fairly even distribution of the CO in the blood

The random error of a single determination of the total amount of haemoglobin was calculated from duplicate determinations to be $\pm 5\,5$ g ($n = 10$) This error is comparatively large compared with isotope techniques [6]. The procedure used could however easily be added to a preceding determination of the CO elimination and allowed a rapid estimation of the haemoglobin mass. This was a great advantage in situations when the investigation had to be completed rapidly before an exchange transfusion

Determination of the serum bilirubin concentration

Total serum bilirubin was determined according to the method of Jendrassik-Cleghorn [34] with the simplified modification described by Jendrassik and Gróf [35] In the reaction 0 1 ml serum or diluted serum, 0 4 ml caffeine mixture and 0 1 ml Diazo reagent were used The patient's serum with caffeine mixture and water was used as blank. The extinction was read after 15 min at 530 $m\mu$ in a Beckman B spectrophotometer with voltage stabilizer The method was standardized with dilutions of commercial bilirubin (Merck AG Darmstadt) in serum Standardization was repeated regularly and the extinction of the bilirubin preparation was found to be very constant A control serum (Versatol Paediatric) was used on each occasion of analysis The mean value for these analyses agreed well with the concentration given by the manufacturer The standard deviation of the determinations of the control sera was 0 3 mg per 100 ml Each unknown serum was analyzed in duplicate and the random error of a single determination was $\pm 0\,4$ mg per 100 ml

The amount of directly reacting bilirubin was also determined Except in some cases of Rh haemolytic disease only small amounts were found Since the total bilirubin is probably the best index of bilirubin production only the values for total bilirubin were used in this presentation

Determination of the haemoglobin concentration in blood

Haemoglobin was determined as oxyhaemoglobin after addition of sodium carbonate (0.02 ml blood and 3.98 ml 0.1 per cent Na_2CO_3). The extinction was read in a Beckman B spectrophotometer at 540 mμ with water as blank. The method was standardized with haemoglobin solutions determined by means of their oxygen combining capacity On each occasion of analysis a known haemoglobin solution was included as control. The standard deviation of the extinction for the control solution corresponded to 0.26 g haemoglobin per 100 ml

The random error of the method determined from the difference between two capillary samples was found to be ±0.3 g per 100 ml. When duplicate enous samples were analyzed the ariation was of the same magnitude as between duplicate capillary samples.

Determination of the number of reticulocytes

The percentage of reticulocytes was counted on a smear after vital staining for at least 20 min with brilliant cresyl blue. One thousand or more erythrocytes were counted with 1000x magnification. The random error of the method was calculated from the difference between t o smears from the same patient and was found to be ±1.5 reticulocytes per 1000 counted cells

The determinations of the bilirubin and haemoglobin concentrations and the number of reticulocytes were performed in the Department of Clinical Chemistry the Children hospital.

The blood grouping and serological tests were done ith standard techniques in the Blood Bank, Sahlgren Hospital

RESULTS AND DISCUSSION

PART I. GENERAL ASPECTS ON THE CO METABOLISM IN NEWBORN INFANTS

On the influence of exogenous CO on the COHb level in blood

During pregnancy the CO tension in the maternal blood influences the COHb level in the fetus [24]. A mother who is a smoker may increase the COHb level of her fetus considerably and this effect will last one or two days after birth. With few exceptions no infants of smoking mothers were included in the present investigation and the influence of exogenous CO after birth was therefore limited to the effect of the CO content in the inspired air In order to determine the magnitude of this contribution to the COHb level the CO concentration in room air from the Children s hospital was determined systematically during one year Air was collected between 8 and 10 o clock in the morning twice a week on randomly chosen days from the ward caring for the newborn infants. During the first months air from one ward in the Obstetric Department, Sahlgren s Hospital, collected on the same days and at the same time in the morning was analyzed The CO concentration in the Children s hospital was also determined each day during some weeks and repeated determinations were done on some days.

The CO concentrations in room air from the Children s hospital during the period August 1966 to July 1967 are shown in Table 1

Table 1 CO concentration (ppm) in air from the Children s hospital, Göteborg during the period August 1966 to July 1967 As comparison the results of tw earlier investigations are given.

Göteborg Month		mean	S.D.	range
JAN	9	1 08	0.59	0 4-2.5
FEB	8	0.96	0.50	0.5-2.1
MAR	8	1.29	0.92	0 7 3.5
APR	9	0 72	0.18	0.4-1.0
MAY	8	0 69	0.11	0.5-0 8
JUN	9	0.54	0 09	0.4-0.7
JUL	9	0.60	0.26	0 4-1 1
AUG	9	0 66	0.35	0.4-1.5
SEP	9	0.72	0.32	0.4-1.3
OCT	8	1.01	0 42	0.7 1 9
NOV	9	1.28	0 47	0 8-[illegible]
DEC	8	1.63	0.90	0.5-3.2
TOTAL	103	0.92	0.57	0.4-3.5
Uppsala (Wranne)				0 2 1.5
Philadelphia (Coburn *et al.*)		2.2	0.98	0.4-4.5

CO concentration in the gas mixture The COHb level in blood was measured before and after CO breathing. The total amount of haemoglobin was calculated from the increase of the CO saturation in blood and the amount of CO absorbed using 1.34 ml CO per g as the CO combining capacity of haemoglobin

The value 1.34 is obtained using 66 400 for the molecular weight of haemoglobin. However this has recently been calculated to be 64 458 [7], corresponding to a CO capacity of 1.39 ml per g haemoglobin. Since the haemoglobin method was standardized with haemoglobin solutions determined by their oxygen capacity the COHb values are not influenced by the value for the haemoglobin molecular weight. The total amount of haemoglobin determined by the CO-method would decrease 3.5 per cent, if the factor 1.39 was used.

The distribution of CO in the body is determined by the amounts of different haemoproteins and their relative affinities for CO The main part of the CO is bound to circulating haemoglobin and equilibrium is reached rapidly in the blood [43] The extravascular CO pool mainly consists of CO bound to myoglobin. The size of this pool has been estimated from simultaneous determinations of the blood volume by a CO dilution technique and by dilution of isotope labelled red cells to 16 ± 10 per cent in man [49] Equilibrium between intravascular and extravascular CO pools is reached within 15–45 min in dogs [43] Sjöstrand estimated that with his rebreathing CO method about 5 per cent of administered CO was bound to extravascular haemoproteins after 15 min rebreathing [62]. In the present procedure the extravascular CO loss was probably of less importance since the CO exposure was shorter and the initial alveolar CO tension lower than in the rebreathing method Furthermore the relative amount of myoglobin is smaller in newborns than in adults [33]

During the period of CO breathing the circulating erythrocytes can be assumed to pass the pulmonary capillaries several times, which should allow a fairly even distribution of the CO in the blood

The random error of a single determination of the total amount of haemoglobin was calculated from duplicate determinations to be ± 5.5 g ($n = 10$) This error is comparatively large compared with isotope techniques [6]. The procedure used could, however easily be added to a preceding determination of the CO elimination and allowed a rapid estimation of the haemoglobin mass. This was a great advantage in situations when the investigation had to be completed rapidly before an exchange transfusion

Determination of the serum bilirubin concentration

Total serum bilirubin was determined according to the method of Jendrassik-Cleghorn [34] with the simplified modification described by Jendrassik and Gróf [35] In the reaction 0 1 ml serum or diluted serum 0 4 ml caffeine mixture and 0 1 ml Diazo reagent were used The patient's serum with caffeine mixture and water was used as blank The extinction was read after 15 min at 530 mμ in a Beckman B spectrophotometer with voltage stabilizer The method was standardized with dilutions of commercial bilirubin (Merck AG Darmstadt) in serum Standardization was repeated regularly and the extinction of the bilirubin preparation was found to be very constant A control serum (Versatol Paediatric) was used on each occasion of analysis The mean value for these analyses agreed well with the concentration given by the manufacturer The standard deviation of the determinations of the control sera was 0 3 mg per 100 ml Each unknown serum was analyzed in duplicate and the random error of a single determination was ± 0.4 mg per 100 ml

The amount of directly reacting bilirubin was also determined Except in some cases of Rh haemolytic disease only small amounts were found. Since the total bilirubin is probably the best index of bilirubin production, only the values for total bilirubin were used in this presentation

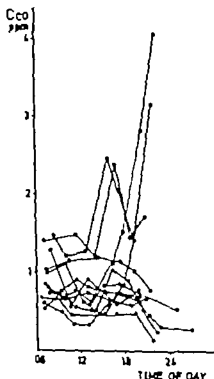


Fig. 4. Variation in room air CO concentration during the same day

actually of the same magnitude as the variation encountered in healthy newborns (I, II) and adults (V). The influence of exogenous CO was probably not of that great importance. Because of the time constant for equilibrium between air and blood peak CO concentrations in air of short duration do not increase the CO saturation of blood as much as indicated by Haldane's equation. Furthermore it is possible that these peaks represented a contamination with combustible gases other than CO

On the relationship between the COHb level in blood and the pulmonary CO elimination (IV)

It can be assumed that in most of the infants the COHb level was determined mainly by the endogenous formation and the elimination of CO. Impaired CO elimination leads to increased COHb levels and it was essential to investigate this possibility in the newborn infants. In full-term infants without signs of respiratory disease increased COHb levels were always found in connection with an increased pulmonary CO elimination. This was true from the first day after birth and also in the presence of haemolytic disease with anaemia (IV). The positive correlation between COHb and CO elimination in newborns permits the conclusion that the increased COHb levels found in many infants did not depend on an impaired CO elimination in comparison with other newborns.

It was also of interest to evaluate the efficiency of the CO elimination in newborn infants compared with that in adults. The values for the alveolar ventilation and the pulmonary diffusing capacity during the first week of life compare favourably with adult values related to body size [37]. They indicate that the pulmonary CO elimination in the newborn should be at least as efficient as that in the adult. This conclusion was supported by the results of determinations of the COHb level in infants after measuring the total amount of haemoglobin with the CO-method. The half time of elimination of the extra CO was $2.5^{1}{}_{2}$ hours, which is shorter than in adults [55] (Fig. 5).

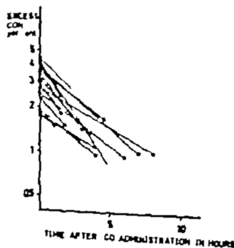


Fig. 5. COHb level in blood after exposure to CO, x=time after exposure, y=difference between the measured and initial COHb levels.

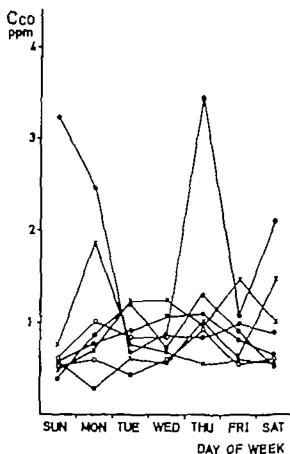


Fig. 3 Variation in room air CO concentration (C_{CO}) during the same week.

The distribution of the values was skew and therefore the standard deviations given in the table cannot be used with certainty for estimation of the confidence intervals It was estimated from tables of distribution-free tolerance limits [69] that 95 per cent of the CO concentrations could be assumed to fall within the range given for the whole period (γ=0 99)

A considerable variation was found from day to day during the same week (Fig. 3) and also during the same day a marked variation could be found (Fig. 4)

The room air CO concentration in the Obstetric Department was lower than that in the Children's hospital Mean values and standard deviations for the determinations in the two hospitals from the same day were 0 78±0 42 ppm (range 0.35—1 99) and 1 07± 0 55 ppm (range 0 35—2.46) respectively ($n=31$)

The COHb level corresponding to the CO concentration in inspired air ($COHb_{ex}$) was calculated from Haldane's equation assuming P_{CO} to be 93 mm Hg and O_2Hb 98 per cent [37] and using the value 210 for the equilibrium constant [58] The room air CO concentration in the Children's hospital on the average corresponded to 0 15 per cent COHb (range 0 06—0 55 per cent), which constitutes about one fifth of the level found in healthy newborns Assuming that the relation between the CO concentrations in the Children's hospital and the Obstetric Department was constant during the year the average influence of exogenous CO in the Obstetric Department can be estimated to be 0 10 per cent COHb

The CO content in hospital air in this city was somewhat higher than that reported from Uppsala [76] but lower than that in Phila delphia [12] (Table 1) The calculated value for COHb should be regarded as an approxi mate estimation of the influence of the exogenous CO on the COHb The non-specificity of the Hopcalite CO method is probably of greater importance during the determination of the CO content in the ambient air than in the blood. This implies that the $COHb_{ex}$ might have been overestimated The accuracy of the estimation also depends on to what extent the determined CO concentrations were representative for the period of study A large variation could be found within one day but the majority of repeated determinations fell within a comparatively narrow range (Fig. 4) The morning value was therefore assumed to be an acceptable estimate of the mean level for the day Except for the increase of the traffic outside the hospital there was no change in the local conditions during the period of investigation which could be suspected to influence the degree of air pollution in the wards The CO concentrations in the Children's hospital during two earlier periods agreed well with those reported here Although the estimated average influence of the exogenous CO was relatively small the range of this influence was considerable The variation of the COHb level in blood corresponding to the range of the CO concentrations in air was

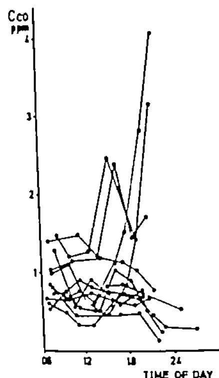


Fig. 4. Variation in room air CO concentration during the same day

actually of the same magnitude as the variation encountered in healthy newborns (I, II) and adults (V). The influence of exogenous CO was probably not of that great importance. Because of the time constant for equilibrium between air and blood peak CO concentrations in air of short duration do not increase the CO saturation of blood as much as indicated by Haldane's equation. Furthermore it is possible that these peaks represented a contamination with combustible gases other than CO.

On the relationship between the COHb level in blood and the pulmonary CO elimination (IV)

It can be assumed that in most of the infants the COHb level was determined mainly by the endogenous formation and the elimination of CO. Impaired CO elimination leads to increased COHb levels and it was essential to investigate this possibility in the newborn infants. In full-term infants without signs of respiratory disease increased COHb levels were always found in connection with an increased pulmonary CO elimination. This was true from the first day after birth and also in the presence of haemolytic disease with anaemia (IV). The positive correlation between COHb and CO elimination in newborns permits the conclusion that the increased COHb levels found in many infants did not depend on an impaired CO elimination in comparison with other newborns.

It was also of interest to evaluate the efficiency of the CO elimination in newborn infants compared with that in adults. The values for the alveolar ventilation and the pulmonary diffusing capacity during the first week of life compare favourably with adult values related to body size [37]. They indicate that the pulmonary CO elimination in the newborn should be at least as efficient as that in the adult. This conclusion was supported by the results of determinations of the COHb level in infants after measuring the total amount of haemoglobin with the CO-method. The half time of elimination of the extra CO was 2 $5^1/_2$ hours, which is shorter than in adults [55] (Fig. 5).

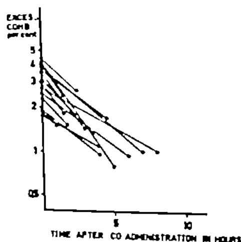


Fig. 5. COHb level in blood after exposure to CO, x = time after exposure, y = difference between the measured and initial COHb levels.

Coburn *et al* also found a correlation between the COHb level and the CO production in adults with haemolytic disease [12]. The random error of an estimate of the endogenous CO formation from the COHb level was however large, ±0 80 ml CO per hour corresponding to ±46 per cent of the mean. According to Coburn *et al* the variation in the relation between COHb and CO production could not be explained by the errors of the methods employed but could be attributed to the influence of variations in the alveolar ventilation and pulmonary diffusing capacity They concluded that COHb is of limited value as a predictor of the endogenous CO formation in the individual case.

The correlation between the COHb level and the pulmonary CO elimination in newborn infants was good ($r=0\ 90$) The random error of an estimate of the CO elimination from the COHb was ±4 0 μl per 10 min, or ±33 per cent of the mean About one fourth of this variation could be explained by the error in the determination of CO elimination If the COHb level was related to the CO elimination per kg body weight the correlation coefficient was 0 91 and the error of an estimation of the CO elimination ±25 per cent (Fig. 6) In a steady state the pulmonary CO elimination approximately equals the endogenous CO formation In this situation the COHb level should be a fairly good predictor of the CO production in the body

Coburn *et al* did not take the body size into consideration in their calculations [12]. They do not give the weight of their patients, but the reported values for total haemoglobin and venous haemoglobin concentration indicate a large variation in the blood volume (3 5—6 9 l) which should imply a large variation in the body size It is possible that this factor caused part of the large variation in the relation between COHb and CO production which they found In a later communication data were presented allowing calculation of CO production per kg [14] These values have been plotted in Fig. 6 and their relation to the COHb level agreed well with that found in newborns.

On the relationship between the COHb level and the rate of haemolysis (II V)

If exposure to CO can be avoided and the pulmonary function is normal the COHb level in blood will reflect the endogenous CO formation The association between increased COHb levels and increased haemolysis has repeatedly been demonstrated in adults (14 18, 29 51 63] and also in isolated investigations on newborns [1 50] This finding was verified by the present investigation which showed markedly increased COHb levels in Rh haemolytic disease of the newborn (II) The COHb level was significantly correlated to the severity of the disease Thus in 17 of 21 infants with COHb levels exceeding the normal mean level by more than 2 S.D during the first hours after birth the bilirubin concentration increased by more than 0 5 mg per 100 ml per hour In infants with lower COHb the rate of bilirubin increase was slower This indicates that there is a close association between COHb and the rate of haemolysis

A significant correlation was found between the COHb level and the CO elimination per g haemoglobin ($r=0\ 69$), which can be assumed to reflect the rate of haemolysis (V) The random error of an estimate of the rate of haemolysis from COHb was however considerable, ±48 per cent of the mean This variation was partly explained by the large errors in the determination of the CO elimination and total haemoglobin but must be considered when the COHb levels are evaluated A comparison with earlier investigations on adults [12, 14 18] showed a good agreement between the investigations with approximately the same degree of correlation between the two variables. The comparison suggested a curvilinear regression of COHb upon the rate of haemolysis. The combined results were found to fit best an equation of the type $y=a+bx^{\frac{1}{2}}$ The equation calculated from the results of the present

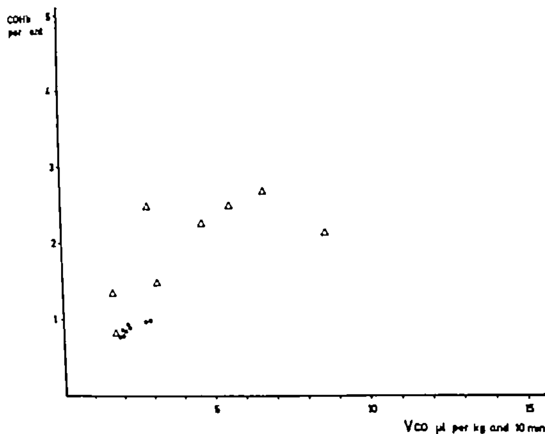


Fig. 6. The relationship between CO elimination per kg (x) and COHb (y). Open circles infants with probable exposure to CO. Filled circles infants with no exposure to CO. Triangles adults (calculated from Coburn *et al.* 1966). Regression equation for the infants
y = 0.30x + 0.25, r = 0.91

investigation was described by $y = 0.31 + 1.71x^{1}$ (x = CO elimination in µl per g haemoglobin per 10 min, y = COHb in per cent). However further investigations are necessary to establish the relationship between the two variables.

Coburn *et al.* have derived equations describing the major physiological variables determining the COHb level in blood under steady state conditions and the change of COHb when any of the several variables are suddenly altered [12]. The following equation is assumed to describe the steady state

$$COHb_{\infty} = \frac{V_{CO} M(O_2Hb)}{\bar{P}c_{O_2}} \times \left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}} \right] \quad (3)$$

V_{CO} = rate of endogenous CO formation in ml STPD per min

M = equilibrium constant in Haldane's equation

O_2Hb = mean pulmonary capillary oxygen saturation in per cent

$\bar{P}c_{O_2}$ = mean pulmonary capillary oxygen tension in mm Hg

D_L = pulmonary diffusing capacity for CO in ml STPD per min per mm Hg

P_B = barometric pressure

P_{H_2O} = vapor pressure of water at 37 C

V_A = alveolar ventilation in ml STPD per min

Since the rate of haemolysis is expressed by the CO production/total haemoglobin ratio the following equation for the relation between COHb and haemolysis can be derived

$$COHb_{ml} = \frac{V_{CO}}{THb} \times \frac{M(O_2Hb)}{P_{CO_2}} \times \left[\frac{THb}{D_L} + \frac{THb(P_B - P_{H_2O})}{V_A}\right] \quad (4)$$

THb = total amount of haemoglobin in g

In the absence of cardiopulmonary disease $\frac{M(O_2Hb)}{P_{CO}}$ can be assumed to be constant

THb is a function of the blood volume and the haemoglobin concentration The equation can therefore be written

$$COHb_{ml} = K_1 \times \frac{V_{CO}}{THb} \times Hb \times \left[\frac{10BV}{D_L} + \frac{10BV(P_B - P_{H_2O})}{V_A}\right] \quad (5)$$

Hb = venous haemoglobin concentration in g per 100 ml

BV = blood volume in l

The numerical value of the constant K_1 is to some degree dependent on the haemoglobin concentration

BV V_A and D_L are all related to the body size This will reduce the influence of the body size on the terms within the brackets. If these terms are regarded as a constant, equation (5) can be simplified to

$$COHb_{ml} = K_2 \times \frac{V_{CO}}{THb} \times Hb \quad \text{or} \quad (6)$$

$$\frac{COHb_{ml}}{Hb} = K_2 \times \frac{V_{CO}}{THb} \quad (7)$$

BV is well correlated to the body weight, while the relationship between V_A or D_L and body size changes with the age of the individual The value of the constant K_2 therefore varies with age

If V_{CO} is expressed in μl per 10 min, the constant in equation (7) can be calculated to be 0 133 assuming M = 210 O_2Hb = 98 per cent P_{CO_2} = 93 mm Hg, D_L = 2.1 ml per mm Hg per min, V_A = 440 ml per min, BV = 90 ml per kg the body weight = 3 5 kg, and the body/venous haematocrit ratio = 0 91 [6, 37 58]

The relation between $\frac{V_{CO}}{THb}$ (x) and $\frac{COHb}{Hb}$ (y) calculated from the results of the present investigation (V) was described by $\hat{y}$ = 0 144x + 0 028 with r = 0 73 and the random error of an estimate of haemolysis ±46 per cent. The blood volume in infants with Rh haemolytic disease 65 ml per kg (V), was much lower than in the other groups. If the infants with Rh haemolytic disease were excluded the observed equation was $\hat{y}$ = 0 146x + 0 025 r = 0 89 and the error of an estimate of haemolysis ± 33 per cent. The value of the constant in equation (7) for BV = 65 ml per kg was calculated to be 0 096 The observed equation for the infants with Rh haemolytic disease was $\hat{y}$ = 0 102x + 0 049 with r = 0 39 and the error of an estimate of haemolysis ±37 per cent. The calculated and the observed values of the constant K_2 thus agreed well The effect of the blood volume on the numerical value of this constant was clearly demonstrated in the present material. The low blood volume in Rh haemolytic disease partly depended on an early clamping of the cord but was also an effect of the anaemia. The haemoglobin concentration also influences the size of the constant through its effect on the pulmonary diffusing capacity but this effect was probably of less importance

According to equation (7) the COHb level is directly proportional to the rate of haemolysis at a constant haemoglobin concentration In the case of anaemia the rate of haemolysis is

underestimated by the COHb level. This influence of the haemoglobin concentration on the relation between COHb and haemolysis was in accordance with the suggested curvilinear relation between the two variables (V).

From equation (7) also follows that the COHb level is related to the CO production per kg body weight, which was verified by the results of the present investigation (IV).

PART II. CLINICAL ASPECTS ON THE ENDOGENOUS CO METABOLISM IN NEWBORN INFANTS

On the endogenous CO formation in full-term healthy newborns (I II IV V)

In full-term healthy newborns without jaundice (measured bilirubin concentration below 10 mg per 100 ml) increased COHb levels were found during the first week after birth compared with adult values (Table 2) (I II). The highest COHb values were found in cord blood with a decreasing level during the first 12 24 hours. On the second and third day the COHb level was constant and after this a further decrease towards adult values was seen.

The high COHb level found in cord blood might be explained by an inefficient CO elimination through the placenta or by the effect of the low oxygen tension and pH prevailing at birth on the equilibrium between the CO tension and COHb [37]. Consequently the decreasing COHb level during the first day should depend on a new equilibrium established after birth. Wranne found that more CO was eliminated in the expired air during the first day than on the following days [77]. He estimated that the excess of CO eliminated on the first day was not entirely accounted for by the decrease of the CO pool and suggested that it also reflected the destruction of a population of erythrocytes with increased fragility immediately after birth [60].

The pulmonary CO elimination in newborn infants compared favourably with that in adults from the first day after birth (IV). There is therefore no reason to believe that after the first day the increased COHb level in healthy newborns was an effect of CO retention. Simultaneous determinations of the CO elimination and total haemoglobin in six infants aged 73–127 hours and with bilirubin concentration below 10 mg per 100 ml (case nos ? 7 V) showed that the CO elimination corresponded to the degradation of 1 5 per cent of the haemoglobin mass per day. Wranne came to the same figure in his estimation of the daily haemoglobin catabolism [77]. These findings were in accordance with the results of earlier estimations of the red cell survival in newborn infants, which have practically all demonstrated a shortened life span of the fetal red cells [23 79].

A uniformly reduced red cell survival cannot explain the reduction of the fractional haemoglobin catabolism, suggested by the decreasing COHb level after the third day of life. In a longitudinal investigation during the first week after birth Koch was not able to demonstrate any changes of importance in ventilation, diffusing capacity oxygen tensions or acid-base balance after the first day [37]. It seems therefore unlikely that the decreasing COHb level after the third day should depend on a change of the equilibrium between the CO in the blood and the alveoli. The possibility of a population of fragile red cells disappearing rapidly during the first day(s) has already been mentioned. Other sources for the CO production than circulating erythrocytes must also be considered.

Table 2 COHb level in full-term healthy newborns during the first week compared with that in healthy non-smoking adults

Age		mean	S D
Cord blood	12	1 12	0 14
1–12 hs	13	1.05	0.15
13–24 hs	8	1 02	0 18
25–48 hs	12	0 92	0.13
49–72 hs	14	0.93	0.11
73–96 hs	17	0 77	0.13
97 144 hs	11	0.76	0 10
Adults	11	0.72	0.09

D_L = pulmonary diffusing capacity for CO in ml STPD per min per mm Hg

P_B = barometric pressure

P_{H_2O} = vapor pressure of water at 37 C

V_A = alveolar ventilation in ml STPD per min

Since the rate of haemolysis is expressed by the CO production/total haemoglobin ratio the following equation for the relation between COHb and haemolysis can be derived

$$COHb_{end} = \frac{V_{CO}}{THb} \times \frac{M(O_2Hb)}{\bar{P}c_O} \times \left[\frac{THb}{D_L} + \frac{THb(P_B - P_{H_2O})}{V_A}\right] \quad (4)$$

THb = total amount of haemoglobin in g

In the absence of cardiopulmonary disease $\frac{M(O_2Hb)}{\bar{P}c_O}$ can be assumed to be constant

THb is a function of the blood volume and the haemoglobin concentration The equation can therefore be written

$$COHb_{end} = K_1 \times \frac{V_{CO}}{THb} \times Hb \times \left[\frac{10BV}{D_L} + \frac{10BV(P_B - P_{H_2O})}{V_A}\right] \quad (5)$$

Hb = venous haemoglobin concentration in g per 100 ml

BV = blood volume in l

The numerical value of the constant K_1 is to some degree dependent on the haemoglobin concentration

BV V_A and D_L are all related to the body size. This will reduce the influence of the body size on the terms within the brackets If these terms are regarded as a constant equation (5) can be simplified to

$$COHb_{end} = K_2 \times \frac{V_{CO}}{THb} \times Hb \quad \text{or} \quad (6)$$

$$\frac{COHb_{end}}{Hb} = K_2 \times \frac{V_{CO}}{THb} \quad (7)$$

BV is well correlated to the body weight, while the relationship between V_A or D_L and body size changes with the age of the individual The value of the constant K_2 therefore varies with age

If V_{CO} is expressed in μl per 10 min the constant in equation (7) can be calculated to be 0 133 assuming M = 210 O_2Hb = 98 per cent $\bar{P}c_{O_2}$ = 93 mm Hg, D_L = 2.1 ml per mm Hg per min V_A = 440 ml per min BV = 90 ml per kg, the body weight = 3 5 kg, and the body/venous haematocrit ratio = 0 91 [6, 37 58].

The relation between $\frac{V_{CO}}{THb}$ (x) and $\frac{COHb}{Hb}$ (y) calculated from the results of the present investigation (V) was described by $\bar{y}$ = 0 144x + 0 028 with r = 0 73 and the random error of an estimate of haemolysis ±46 per cent The blood volume in infants with Rh haemolytic disease 65 ml per kg (V), was much lower than in the other groups. If the infants with Rh haemolytic disease were excluded the observed equation was $\bar{y}$ = 0 146x + 0 025 r = 0 89 and the error of an estimate of haemolysis ± 33 per cent The value of the constant in equation (7) for BV = 65 ml per kg was calculated to be 0 096 The observed equation for the infants with Rh haemolytic disease was $\bar{y}$ = 0 102x + 0 049 with r = 0 39 and the error of an estimate of haemolysis ±37 per cent The calculated and the observed values of the constant K_2 thus agreed well The effect of the blood volume on the numerical value of this constant was clearly demonstrated in the present material The low blood volume in Rh haemolytic disease partly depended on an early clamping of the cord, but was also an effect of the anaemia. The haemoglobin concentration also influences the size of the constant through its effect on the pulmonary diffusing capacity but this effect was probably of less importance

According to equation (7) the COHb level is directly proportional to the rate of haemolysis at a constant haemoglobin concentration In the case of anaemia the rate of haemolysis is

underestimated by the COHb level. This influence of the haemoglobin concentration on the relation between COHb and haemolysis was in accordance with the suggested curvilinear relation between the two variables (V).

From equation (7) also follows that the COHb level is related to the CO production per kg body weight, which was verified by the results of the present investigation (IV).

PART II. CLINICAL ASPECTS ON THE ENDOGENOUS CO METABOLISM IN NEWBORN INFANTS

On the endogenous CO formation in full-term healthy newborns (I II IV V)

In full-term healthy newborns without jaundice (measured bilirubin concentration below 10 mg per 100 ml) increased COHb levels were found during the first week after birth compared with adult values (Table 2) (I II). The highest COHb values were found in cord blood with a decreasing level during the first 12 24 hours. On the second and third day the COHb level was constant and after this a further decrease towards adult values was seen.

The high COHb level found in cord blood might be explained by an inefficient CO elimination through the placenta or by the effect of the low oxygen tension and pH prevailing at birth on the equilibrium between the CO tension and COHb [37]. Consequently the decreasing COHb level during the first day should depend on a new equilibrium established after birth. Wranne found that more CO was eliminated in the expired air during the first day than on the following days [77]. He estimated that the excess of CO eliminated on the first day was not entirely accounted for by the decrease of the CO pool and suggested that it also reflected the destruction of a population of erythrocytes with increased fragility immediately after birth [60].

Table 2. COHb level in full-term healthy newborns during the first week compared with that in healthy non-smoking adults

Age		mean	S D
Cord blood	12	1 12	0.14
1 12 hrs	13	1.05	0.15
13–24 hrs	8	1.02	0 18
25–48 hrs	12	0.92	0.13
49–72 hrs	14	0 93	0 11
73–96 hrs	17	0.77	0.13
97–144 hrs	11	0.76	0.10
Adults	11	0.72	0 09

The pulmonary CO elimination in newborn infants compared favourably with that in adults from the first day after birth (IV). There is therefore no reason to believe that after the first day the increased COHb level in healthy newborns was an effect of CO retention. Simultaneous determinations of the CO elimination and total haemoglobin in six infants aged 73–127 hours and with bilirubin concentration below 10 mg per 100 ml (case nos ? 7 V) showed that the CO elimination corresponded to the degradation of 1.5 per cent of the haemoglobin mass per day. Wranne came to the same figure in his estimation of the daily haemoglobin catabolism [77]. These findings were in accordance with the results of earlier estimations of the red cell survival in newborn infants, which have practically all demonstrated a shortened life span of the fetal red cells [23, 79].

A uniformly reduced red cell survival cannot explain the reduction of the fractional haemoglobin catabolism, suggested by the decreasing COHb level after the third day of life. In a longitudinal investigation during the first week after birth Koch was not able to demonstrate any changes of importance in ventilation, diffusing capacity, oxygen tensions or acid-base balance after the first day [37]. It seems therefore unlikely that the decreasing COHb level after the third day should depend on a change of the equilibrium between the CO in the blood and the alveoli. The possibility of a population of fragile red cells disappearing rapidly during the first day(s) has already been mentioned. Other sources for the CO production than circulating erythrocytes must also be considered.

Vest has shown that the early peak of labelled bilirubin after administration of ^{15}N glycine is large in newborn infants [71]. The formation of early labelled bilirubin is to a large extent dependent on the erythropoietic activity A very lively erythropoiesis is found during the last period of intrauterine life and continues during the first days after birth [36] After about three days the erythropoietic activity in the marrow suddenly decreases, manifested by a drop in the reticulocyte count [57] These changes coincide with the decrease of the COHb level found in this investigation Thus it is possible that the increased COHb level during the first days partly reflected an increased CO formation associated with the erythropoiesis.

On the endogenous CO formation in icteric newborns without blood group incompatibility (I III IV V)

In full term newborn infants with jaundice not caused by blood group incompatibility increased COHb level (I III) and increased CO elimination (IV) were found in comparison with non icteric infants In 33 infants with bilirubin concentration 19 3±8 1 mg per 100 ml (range 6 0—35.2) on the fourth—sixth day after birth the COHb level was 1 02±0 25 per cent (mean ±S D) Both the COHb level and the CO elimination were significantly correlated to the bilirubin concentration ($r = 0\ 76$ and 0 73 respectively) In five infants (case nos 8–12, V) with bilirubin concentration 10 9–27 8 mg per 100 ml (mean 16 6) simultaneous determinations of the CO elimination and total haemoglobin showed an average CO elimination corresponding to the destruction of 2.4 per cent of the haemoglobin mass per day These findings indicate that an increased bilirubin production contributed to the hyperbilirubinaemia in this group of infants.

Practically all newborns have increased serum bilirubin concentrations compared with adults and visible jaundice is very common The problem of neonatal jaundice has been extensively reviewed in several monographs [8, 39 56]. In the fifties the nature of the bilirubin pigments was clarified in more detail and evidence was presented for a deficient hepatic conjugation and excretion of bilirubin in newborn infants [8 56]. This mechanism is generally accepted as the common denominator of neonatal jaundice and is assumed entirely to account for the hyperbilirubinaemia in many infants

In most cases the jaundice appears on the second or third day after birth reaches its maximum within a further two or three days and then subsides. There are many factors which influence the course and intensity of the hyperbilirubinaemia and by experience certain criteria have been established indicating the existence of such factors in the individual case Jaundice observed on the first day is often explained by a haemolytic disease If the bilirubin concentration reaches a high level, an underlying disease is often suspected, but there is considerable uncertainty about which level should be regarded as pathological.

In the present group of icteric newborns the clinical course was of no concern except that the bilirubin concentration in some infants reached a high level Blood group incompatibility was excluded in the selection of infants as well as some other factors known to predispose the infant to hyperbilirubinaemia such as maternal diabetes immaturity anoxia and melena [39 46 56]. The small amounts of vitamin K given to the infants should not interfere with the red cell metabolism [79] None of the infants displayed signs of infection Asymptomatic infections have been found in infants with increased bilirubinaemia [16], and this possibility was not excluded systematically Routine haematological investigation did not suggest a haemolytic disease, but no comprehensive investigation was done to diagnose other haemolytic diseases than those caused by iso-immunization.

However it is not likely that an increased bilirubin production in the present group was caused by specific haemolytic diseases,

and an alternative explanation of the hyper bilirubinaemia seems more attractive. In the previous section it was mentioned that increased haemoglobin catabolism was a regular finding in healthy newborns. In some infants this physiologic process might be exaggerated leading to a marked hyperbilirubinaemia. The fact that the same relation between the COHb level and the bilirubin concentration was found at different bilirubin levels (III) speaks in favour of this hypothesis. One has not been able to find a correlation between the red cell survival and the bilirubin level in newborn infants [72]. It is therefore possible that neonatal jaundice is caused partly by "shunt" bilirubin, that is bilirubin formation associated with the erythropoiesis or with the degradation of other haemoproteins than haemoglobin.

On the endogenous CO formation in Rh haemolytic disease of the newborn (II IV V)

In Rh haemolytic disease of the newborn very high COHb levels were often found (II). If the bilirubin or haemoglobin concentration at birth necessitated exchange transfusion, the COHb level during the first 12 hours was found to be 2.04±0.96 per cent (range 0.78—5.08 per cent). In other haemolytic conditions, in the absence of exposure to CO, the COHb values in the upper range are rare. According to the equation given above, the mean value corresponded to more than a tenfold increase of erythrocyte destruction (V), which was in agreement with the results of earlier red cell survival studies in this disease [44]. In 22 of the 26 infants requiring exchange transfusion on the first day after birth the COHb level exceeded the normal mean level by more than two S.D. In the four infants with low COHb the rate of bilirubin increase was comparatively slow less than 0.5 mg per 100 ml per hour

The COHb values in cord blood were lower and often fell within the normal range even if the infant demonstrated definite signs of haemolytic disease (II). In infants followed by repeated COHb determinations the COHb level was found to increase significantly after birth. There was a significant correlation between the COHb level and the pulmonary CO elimination in Rh haemolytic disease on the first day ($r = 0.94$) as well as on the following days ($r = 0.68$) (IV). Practically the same relationship was found between the two variables in these infants as in other groups of full-term newborns. This indicates an efficient CO elimination in Rh haemolytic disease and it is unlikely that the increasing COHb level after birth was an effect of CO retention. There seems to be no other explanation for the increasing COHb than an accelerated CO production. At birth there is a far-reaching adjustment of the circulation to extrauterine life with for instance an improved blood flow through the liver. This may imply an increased removal and destruction of the sensitized red cells, explaining a rising CO production.

Infants fulfilling the serological criteria for Rh haemolytic disease but with haemoglobin and bilirubin concentrations at birth not requiring exchange transfusion had normal or slightly increased COHb levels during the first day. After the first day however definitely increased COHb values were found in most of these infants (range 0.49—2.24 per cent). Several infants demonstrated an increasing COHb level at repeated analyses. Although there was a significant correlation between the COHb and the bilirubin concentration ($r = 0.65$), increased COHb values without marked hyperbilirubinaemia were found in some infants indicating a compensated haemolysis.

The COHb level in Rh haemolytic disease was significantly correlated *to the variables* generally used *to evaluate the severity of the* disease, such as the *bilirubin* concentration, haemoglobin concentration and the number of reticulocytes. In medical practice the relation *between the COHb level and the rate of bilirubin increase is* of special interest, since it is essential to evaluate the risk of kernicterus in every case of haemolytic disease of the newborn. *If the COHb level* exceeded the normal mean

Vest has shown that the early peak of labelled bilirubin after administration of ^{15}N glycine is large in newborn infants [71] The formation of early labelled bilirubin is to a large extent dependent on the erythropoietic activity A very lively erythropoiesis is found during the last period of intrauterine life and continues during the first days after birth [36] After about three days the erythropoietic activity in the marrow suddenly decreases manifested by a drop in the reticulocyte count [57]. These changes coincide with the decrease of the COHb level found in this investigation. Thus it is possible that the increased COHb level during the first days partly reflected an increased CO formation associated with the erythropoiesis.

On the endogenous CO formation in icteric newborns without blood group incompatibility (I III IV V)

In full term newborn infants with jaundice not caused by blood group incompatibility increased COHb level (I III) and increased CO elimination (IV) were found in comparison with non icteric infants In 33 infants with bilirubin concentration 19 3±8 1 mg per 100 ml (range 6 0—35 2) on the fourth—sixth day after birth the COHb level was 1 02±0 25 per cent (mean ±S D) Both the COHb level and the CO elimination were significantly correlated to the bilirubin concentration ($r = 0$ 76 and 0 73 respectively) In five infants (case nos 8–12, V) with bilirubin concentration 10 9–27 8 mg per 100 ml (mean 16 6) simultaneous determinations of the CO elimination and total haemoglobin showed an average CO elimination corresponding to the destruction of 2.4 per cent of the haemoglobin mass per day These findings indicate that an increased bilirubin production contributed to the hyperbilirubinaemia in this group of infants

Practically all newborns have increased serum bilirubin concentrations compared with adults and visible jaundice is very common The problem of neonatal jaundice has been extensively reviewed in several monographs [8 39 56] In the fifties the nature of the bilirubin pigments was clarified in more detail and evidence was presented for a deficient hepatic conjugation and excretion of bilirubin in newborn infants [8 56] This mechanism is generally accepted as the common denominator of neonatal jaundice and is assumed entirely to account for the hyperbilirubinaemia in many infants

In most cases the jaundice appears on the second or third day after birth reaches its maximum within a further two or three days and then subsides There are many factors which influence the course and intensity of the hyperbilirubinaemia and by experience certain criteria have been established indicating the existence of such factors in the individual case Jaundice observed on the first day is often explained by a haemolytic disease If the bilirubin concentration reaches a high level, an underlying disease is often suspected but there is considerable uncertainty about which level should be regarded as pathological.

In the present group of icteric newborns the clinical course was of no concern except that the bilirubin concentration in some infants reached a high level. Blood group incompatibility was excluded in the selection of infants as well as some other factors known to predispose the infant to hyperbilirubinaemia such as maternal diabetes, immaturity anoxia and melena [39 46 56] The small amounts of vitamin K given to the infants should not interfere with the red cell metabolism [79] None of the infants displayed signs of infection Asymptomatic infections have been found in infants with increased bilirubinaemia [16], and this possibility was not excluded systematically Routine haematological investigation did not suggest a haemolytic disease, but no comprehensive investigation was done to diagnose other haemolytic diseases than those caused by iso-immunization

However it is not likely that an increased bilirubin production in the present group was caused by specific haemolytic diseases,

ABO compatible infants [II]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated (r=0.91), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4–6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the hyperbilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease, and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism, irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative information about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al.* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al.* The influence of exogenous CO is of particular importance since it may be extremely variable and may

level by more than 2 S D during the first day the bilirubin concentration rose rapidly in most infants A lower COHb value seemed to exclude a rapid rise of the bilirubin concentration but not a high bilirubin level on the following days After the first day the association between the COHb and the rate of bilirubin increase was less marked

Rh haemolytic disease was the only group investigated in which significant anaemia occurred It is therefore possible that the COHb/Hb ratio would have been a better index of haemolysis in this group The bilirubin production is however also related to the haemoglobin concentration and therefore COHb should be preferred as a predictor of the rate of bilirubin increase

On the endogenous CO formation in infants of ABO heterospecific pregnancies (III IV V)

About one fifth of all pregnancies are ABO heterospecific, that is the maternal serum contains natural agglutinins against the ABO antigens of the fetal red cells In many cases anti A and/or anti B with "immune" properties and capable of passing the placental barrier can also be demonstrated in the maternal serum [20, 38]. The ABO antigens are usually well developed at birth in full term infants although not of adult strength [28]. Therefore increased haemolysis due to ABO incompatibility could be expected to be frequent However the haemolytic disease caused by ABO incompatibility is less well defined than Rh haemolytic disease Early jaundice not caused by Rhesus isoimmunization is associated with ABO incompatibility in the majority of cases [30] and haematological and serological studies have provided strong evidence for an immunohaemolytic disease [48 80] An excess of ABO heterospecific pregnancies is also found among infants with jaundice appearing later during the first week [21] but in this case the clinical picture is often indistinguishable from the common neonatal hyperbilirubinaemia.

Infants selected because of jaundice associated with ABO incompatibility had significantly higher COHb levels than normal full term newborns (III) The highest values were found on the first days after birth. The mean ± S D on the second day was 1 73 ± 0 38 per cent and on the third day 1 51 ± 0.30 per cent. In the majority of these infants the early onset of the jaundice and the finding of an increased number of reticulocytes and/or spherocytes suggested a haemolytic disease. The COHb level definitely indicated a rapid rate of erythrocyte destruction in this group Infants investigated after the third day did not display signs of a haemolytic disease to the same degree, and in most cases the picture did not differ from the common hyperbilirubinaemia of the newborn. In this group the bilirubin concentration was 23 4 ± 6 4 mg per 100 ml (range 10 0–36.2) and the COHb level 1 23 ± 0.28 per cent. Since increased COHb values were also found in icteric infants of this age without blood group incompatibility a comparison of the groups was of interest. The relation between COHb and bilirubin in the two groups differed significantly with higher average COHb at a given bilirubin level in ABO incompatibility This indicates that increased haemoglobin catabolism was more important for the development of jaundice in ABO incompatibility than in the other group

Full term healthy newborns of ABO heterospecific pregnancies selected without regard to the bilirubin concentration were compared with a similar group of infants without blood group incompatibility (III) The COHb level was only slightly higher in the former group but after the third day of life the difference between the groups (0 08 per cent COHb) was statistically significant This finding may reflect an increased haemoglobin catabolism due to the ABO incompatibility The small differences must however be interpreted cautiously with regard to the many factors influencing the COHb level Thus, Wranne was not able to show any difference between the CO elimination in "ABO incompatible" infants and that in

ABO compatible infants [77]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r=0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4–6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the bilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease, and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism, irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative information about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al*. The influence of exogenous CO is of particular importance since it may be extremely variable and may

level by more than 2 S D during the first day the bilirubin concentration rose rapidly in most infants A lower COHb value seemed to exclude a rapid rise of the bilirubin concentration but not a high bilirubin level on the following days After the first day the association between the COHb and the rate of bilirubin increase was less marked

Rh haemolytic disease was the only group investigated, in which significant anaemia occurred It is therefore possible that the COHb/Hb ratio would have been a better index of haemolysis *in this* group The bilirubin production is, however also related to the haemoglobin concentration and therefore COHb should be preferred as a predictor of the rate of bilirubin increase.

On the endogenous CO formation in infants of ABO heterospecific pregnancies (III IV V)

About one fifth of all pregnancies are ABO heterospecific, that is the maternal serum contains natural agglutinins against the ABO antigens of the fetal red cells In many cases anti A and/or anti B with immune" properties and capable of passing the placental barrier can also be demonstrated in the maternal serum [20 38] The ABO antigens are usually well developed at birth in full-term infants although not of adult strength [28] Therefore increased haemolysis due to ABO incompatibility could be expected to be frequent. However the haemolytic disease caused by ABO incompatibility is less well defined than Rh haemolytic disease Early jaundice not caused by Rhesus isoimmunization is associated with ABO incompatibility in the majority of cases [30] and haematological and serological studies have provided strong evidence for an immunohaemolytic disease [48 80] An excess of ABO heterospecific pregnancies is also found among infants with jaundice appearing later during the first week [21] but in this case the clinical picture is often indistinguishable from the common neonatal hyperbilirubinaemia

Infants selected because of jaundice associated with ABO incompatibility had significantly higher COHb levels than normal full-term newborns (III) The highest values were found on the first days after birth The mean±S.D on the second day was 1 73±0 38 per cent and on the third day 1 51±0 30 per cent. In the majority of these infants the early onset of the jaundice and the finding of an increased number of reticulocytes and/or spherocytes suggested a haemolytic disease The COHb level definitely indicated a rapid rate of erythrocyte destruction in this group Infants investigated after the third day did not display signs of a haemolytic disease to the same degree, and in most cases the picture did not differ from the common hyperbilirubinaemia of the newborn. In this group the bilirubin concentration was 23 4±6.4 mg per 100 ml (range 10 0–36 2) and the COHb level 1.23±0 28 per cent. Since increased COHb values were also found in icteric infants of this age without blood group incompatibility a comparison of the groups was of interest The relation between COHb and bilirubin in the two groups differed significantly with higher average COHb at a given bilirubin level in ABO incompatibility This indicates that increased haemoglobin catabolism was more important for the development of jaundice in ABO incompatibility than in the other group

Full term healthy newborns of ABO heterospecific pregnancies selected without regard to the bilirubin concentration were compared with a similar group of infants without blood group incompatibility (III). The COHb level was only slightly higher in the former group but after the third day of life the difference between the groups (0 08 per cent COHb) was statistically significant This finding may reflect an increased haemoglobin catabolism due to the ABO incompatibility The small differences must however be interpreted cautiously with regard to the many factors influencing the COHb level Thus, Wranne was not able to show any difference between the CO elimination in "ABO incompatible" infants and that in

ABO compatible infants [77]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r = 0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4–6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the bilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative information about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al*. The influence of exogenous CO is of particular importance since it may be extremely variable and may

level by more than 2 S D during the first day the bilirubin concentration rose rapidly in most infants A lower COHb value seemed to exclude a rapid rise of the bilirubin concentration but not a high bilirubin level on the following days. After the first day the association between the COHb and the rate of bilirubin increase was less marked

Rh haemolytic disease was the only group investigated in which significant anaemia occurred It is therefore possible that the COHb/Hb ratio would have been a better index of haemolysis in this group The bilirubin production is, however also related to the haemoglobin concentration and therefore COHb should be preferred as a predictor of the rate of bilirubin increase.

On the endogenous CO formation in infants of ABO heterospecific pregnancies (III IV V)

About one fifth of all pregnancies are ABO heterospecific, that is the maternal serum contains natural agglutinins against the ABO antigens of the fetal red cells In many cases anti A and/or anti B with "immune" properties and capable of passing the placental barrier can also be demonstrated in the maternal serum [20 38] The ABO antigens are usually well developed at birth in full term infants although not of adult strength [28] Therefore increased haemolysis due to ABO incompatibility could be expected to be frequent However the haemolytic disease caused by ABO incompatibility is less well defined than Rh haemolytic disease Early jaundice not caused by Rhesus isoimmunization is associated with ABO incompatibility in the majority of cases [30] and haematological and serological studies have provided strong evidence for an immunohaemolytic disease [48, 80] An excess of ABO heterospecific pregnancies is also found among infants with jaundice appearing later during the first week [21] but in this case the clinical picture is often indistinguishable from the common neonatal hyperbilirubinaemia

Infants selected because of jaundice associated with ABO incompatibility had significantly higher COHb levels than normal full-term newborns (III) The highest values were found on the first days after birth The mean±S.D on the second day was 1 73±0 38 per cent and on the third day 1 51±0 30 per cent. In the majority of these infants the early onset of the jaundice and the finding of an increased number of reticulocytes and/or spherocytes suggested a haemolytic disease. The COHb level definitely indicated a rapid rate of erythrocyte destruction in this group Infants investigated after the third day did not display signs of a haemolytic disease to the same degree, and in most cases the picture did not differ from the common hyperbilirubinaemia of the newborn In this group the bilirubin concentration was 23 4±6.4 mg per 100 ml (range 10 0–36.2) and the COHb level 1.23±0.28 per cent Since increased COHb values were also found in icteric infants of this age without blood group incompatibility a comparison of the groups was of interest The relation between COHb and bilirubin in the two groups differed significantly with higher average COHb at a given bilirubin level in ABO incompatibility This indicates that increased haemoglobin catabolism was more important for the development of jaundice in ABO incompatibility than in the other group

Full-term healthy newborns of ABO heterospecific pregnancies selected without regard to the bilirubin concentration were compared with a similar group of infants without blood group incompatibility (III) The COHb level was only slightly higher in the former group but after the third day of life the difference between the groups (0 08 per cent COHb) was statistically significant This finding may reflect an increased haemoglobin catabolism due to the ABO incompatibility The small differences must however be interpreted cautiously with regard to the many factors influencing the COHb level Thus, Wranne was not able to show any difference between the CO elimination in ABO incompatible" infants and that in

ABO compatible infants [77]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r = 0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4-6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the bilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative information about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al.* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al.* The influence of exogenous CO is of particular importance since it may be extremely variable and may

level by more than 2 S D during the first day the bilirubin concentration rose rapidly in most infants A lower COHb value seemed to exclude a rapid rise of the bilirubin concentration but not a high bilirubin level on the following days. After the first day the association between the COHb and the rate of bilirubin increase was less marked.

Rh haemolytic disease was the only group investigated in which significant anaemia occurred It is therefore possible that the COHb/Hb ratio would have been a better index of haemolysis in this group The bilirubin production is, however also related to the haemoglobin concentration and therefore COHb should be preferred as a predictor of the rate of bilirubin increase

On the endogenous CO formation in infants of ABO heterospecific pregnancies (III IV V)

About one fifth of all pregnancies are ABO heterospecific that is the maternal serum contains natural agglutinins against the ABO antigens of the fetal red cells In many cases anti A and/or anti B with "immune" properties and capable of passing the placental barrier can also be demonstrated in the maternal serum [20 38]. The ABO antigens are usually well developed at birth in full term infants although not of adult strength [28]. Therefore increased haemolysis due to ABO incompatibility could be expected to be frequent However the haemolytic disease caused by ABO incompatibility is less well defined than Rh haemolytic disease Early jaundice not caused by Rhesus isoimmunization is associated with ABO incompatibility in the majority of cases [30] and haematological and serological studies have provided strong evidence for an immunohaemolytic disease [48 80]. An excess of ABO heterospecific pregnancies is also found among infants with jaundice appearing later during the first week [21], but in this case the clinical picture is often indistinguishable from the common neonatal hyperbilirubinaemia.

Infants selected because of jaundice associated with ABO incompatibility had significantly higher COHb levels than normal full-term newborns (III) The highest values were found on the first days after birth The mean±S.D on the second day was 1 73±0 38 per cent and on the third day 1 51±0.30 per cent. In the majority of these infants the early onset of the jaundice and the finding of an increased number of reticulocytes and/or spherocytes suggested a haemolytic disease. The COHb level definitely indicated a rapid rate of erythrocyte destruction in this group Infants investigated after the third day did not display signs of a haemolytic disease to the same degree, and in most cases the picture did not differ from the common hyperbilirubinaemia of the newborn In this group the bilirubin concentration was 23 4±6 4 mg per 100 ml (range 10 0–36 2) and the COHb level 1.23±0.28 per cent. Since increased COHb values were also found in icteric infants of this age without blood group incompatibility a comparison of the groups was of interest. The relation between COHb and bilirubin in the two groups differed significantly with higher average COHb at a given bilirubin level in ABO incompatibility This indicates that increased haemoglobin catabolism was more important for the development of jaundice in ABO incompatibility than in the other group

Full term healthy newborns of ABO heterospecific pregnancies selected without regard to the bilirubin concentration were compared with a similar group of infants without blood group incompatibility (III). The COHb level was only slightly higher in the former group but after the third day of life the difference between the groups (0 08 per cent COHb) was statistically significant This finding may reflect an increased haemoglobin catabolism due to the ABO incompatibility The small differences must however be interpreted cautiously with regard to the many factors influencing the COHb level Thus, Wranne was not able to show any difference between the CO elimination in "ABO incompatible infants and that in

ABO compatible infants [77]. There were however no cases of hyperbilirubinaemia in either group.

In the present study the pulmonary CO elimination was only determined in infants with ABO incompatibility associated with jaundice (IV). The COHb level and CO elimination were significantly correlated ($r = 0.91$), but both were comparatively low with regard to the bilirubin level. The infants selected for elimination studies were therefore probably not representative for the group.

In the infants selected because of jaundice associated with ABO incompatibility a significant correlation was found between COHb and bilirubin on day 3 and days 4–6 (III). In infants with ABO incompatibility selected without regard to the bilirubin level a significant correlation between the two variables was found on day 2 and day 3 but not later. The relation between COHb and bilirubin on the first days after birth was the same in the two groups of infants, indicating a common pathogenesis of the bilirubinaemia only differing in degree.

The results indicate that an increased rate of erythrocyte destruction due to ABO incompatibility is common during the first days after birth. It is sometimes manifested by obvious signs of haemolytic disease, and probably contributes to a hyperbilirubinaemia in many infants.

GENERAL DISCUSSION

A haemolytic disease is often defined as a condition in which the life span of the erythrocytes is decreased. This may lead to accumulation of bilirubin in blood and to anaemia. These and other effects of the increased red cell destruction point to the possibility of a haemolytic disease. Sometimes the specific defect or mechanism responsible for the haemolysis is easily demonstrable, but often the ultimate diagnosis will depend on the demonstration of the decreased red cell survival. In situations with increased red cell destruction in the bone marrow determination of the life span of circulating erythrocytes will not disclose the haemolytic process.

Carbon monoxide is a normal metabolite of haemoglobin and the endogenous CO formation reflects the haemoglobin catabolism irrespective of the site of the red cell destruction. Determination of the endogenous CO production may rapidly give quantitative *information* about the haemoglobin degradation. The determination can be repeated with close intervals and is therefore of particular value in the study of erythrokinetics in non-steady states. Although anaemia is common in haemolytic disease of the newborn and may be deleterious to the infant, hyperbilirubinaemia is the most important effect of increased haemolysis during this period. Bilirubin is formed not only during the degradation of haemoglobin from destroyed erythrocytes but also from other sources. The bilirubin production is probably always accompanied by the formation of equimolar amounts of carbon monoxide. Determination of the endogenous CO formation is therefore of great interest in the evaluation of the pathogenesis of neonatal jaundice.

Direct determination of the endogenous CO formation is a technically difficult and not very precise procedure in small infants. The CO saturation of blood, on the other hand, can be determined easily and with good precision and under certain prerequisite conditions reflects the endogenous CO formation. Coburn *et al* discussed the influence of different factors on the COHb level in blood and concluded that COHb is of limited value as an index of haemolysis [12]. However they did not take into account the variation in body size when they related the COHb level to the endogenous CO production. Several clinical and experimental investigations have demonstrated the value of COHb determinations in the study of haemolytic conditions.

Nevertheless, in the clinical application of the method it is essential to consider the factors discussed by Coburn *et al*. The influence of exogenous CO is of particular importance since it may be extremely variable and may

surpass the effect of the endogenous CO formation considerably Systematic determinations of the CO concentration in room air in the Children s hospital and the Obstetric Department indicated that the average contribution made by exogenous CO to the COHb level was comparatively small, approximately amounting to 15–20 per cent of the normal mean level. Similar determinations should be done in each hospital where COHb is used in the study of haemolytic diseases and should be repeated from time to time. If the CO content in the ambient air is high and variable it can be determined together with the COHb and accounted for

Smokers often have COHb levels far in excess of those found in haemolytic disease Patients should not be allowed to smoke during 1–2 days preceeding an investigation. With regard to the efficient CO elimination found from the first day after birth the COHb level can be used as an index of haemolysis after 1–2 days in an infant whose mother is a smoker

Coburn *et al* stressed the effect of the pulmonary CO elimination on the relation between the COHb level and the endogenous CO production and estimated that possible variations in ventilation and diffusing capacity should influence this relationship considerably [12] The present investigation indicated that in newborn infants without signs of pulmonary disease the influence of these factors was less varying. A close correlation was found between COHb and CO elimination per kg body weight ($r=0.91$) In a steady state the COHb level thus can be assumed to give accurate information about the endogenous CO formation If the CO production increases the COHb level and the CO elimination will rise rapidly and a new steady state is probably reached within a few hours In the case of decreasing CO production the time lag in the CO elimination delays the new equilibrium by about 24 hours.

It has been shown that fetal blood has an increased affinity for oxygen when compared with that of the adult [3] This phenomenon was long assumed to be caused by the fetal haemoglobin but recent investigations indicate that the high affinity does not depend on the fetal haemoglobin *per se* but is a property of the red cells [3] The affinity for oxygen influences the equilibrium described by Haldane s equation In this context the affinity of fetal blood for carbon monoxide is also of importance. Available information on this subject is scanty Engel *et al* have recently reported that fetal haemoglobin has a lower affinity for CO than adult haemoglobin [17], but did not give the difference or describe their experimental procedure. These properties of the fetal blood can be assumed to reduce the numerical value of the constant in Haldane s equation. Direct determination of the constant in fetal blood is however necessary for the estimation of the effect on the COHb level. In this presentation the possible difference between fetal and adult blood has therefore been disregarded

The present investigation has shown that the indirect estimation of the endogenous CO formation from the CO saturation of blood is of value in the study of haemolytic diseases and of the pathogenesis of jaundice in newborn infants. A comparison of groups of patients should disclose even moderate differences in the rate of haemoglobin catabolism especially if the groups are examined under the same environmental conditions In the individual the COHb level reveals an increased haemolysis in the majority of cases. The COHb level also allows a quantification of the rate of haemolysis, but the random error of an estimate of haemolysis from COHb seems to be relatively large.

SUMMARY

Carbon monoxide is a normal metabolite of the haemoproteins and the endogenous formation of CO mainly reflects the haemoglobin catabolism The endogenous CO production was studied in newborn infants indirectly by determination of the CO saturation of blood

(COHb). Several factors may influence the COHb level in blood and the effect of some of these factors was investigated.

The CO content in the ambient air was determined systematically during a period of one year. The average influence of exogenous CO in the Children's hospital was estimated to be approximately 0.15 per cent COHb or about one fifth of the normal mean level.

Simultaneous determinations of the COHb level and the pulmonary CO elimination showed an efficient CO elimination during the newborn period. In newborn infants without respiratory disease increased COHb values are not caused by CO retention.

A significant correlation was found between the COHb level and the rate of haemolysis calculated from the CO elimination and the *total haemoglobin. Theoretical considerations* suggested that the COHb/Hb ratio is a better index of haemolysis than COHb. The results of the present investigation supported this hypothesis. This would imply that in the case of anaemia the COHb level underestimates the rate of haemolysis.

In full-term healthy newborns without appreciable jaundice an increased COHb level was found compared with that in adults. Determination of the CO elimination also indicated an increased haemoglobin catabolism in these infants.

In icteric infants without blood group incompatibility an increased COHb level and CO elimination were found, both significantly correlated to the bilirubin concentration. This indicates that an increased bilirubin production contributed to the hyperbilirubinaemia.

In infants with Rh haemolytic disease very high COHb values were often found. The COHb level was correlated to the severity of the disease. Increased COHb values during the first day after birth were usually associated with a rapid rise of the bilirubin concentration.

Determination of the COHb level in infants of ABO heterospecific pregnancies indicated that an increased haemoglobin catabolism was frequent in connection with ABO incompatibility

REFERENCES

1 Bakowa, S. and Szczepkowski, T. W.. Carbon monoxide in jaundice of the newborn. *Pediat Pol*, 33: 1029. 1958.

2 Barrett, P. V. D. Cline, M. J. and Berlin, N. L. The association of the urobilin early peak and erythropoiesis in man. *J Clin Invest*, 45: 1657. 1966.

3 Bartels, H. Carriage of oxygen in the blood of the foetus, in A.V.S. de Reuck and R. Porter (ed.): *Development of the lung*. J. A. Churchill Ltd, London 1967. p. 276.

4 Bjure, J. Pulmonary diffusing capacity for carbon monoxide in relation to cardiac output in man. *Scand J Clin Lab Invest. Suppl 81*. 1965.

5 Bjure, J. Korsgren, M. and Varnauskas, E. Pulmonary blood volume and diffusing capacity in cardio-pulmonary disease. *Clin Sci*. 33: 225. 1967

6 Bratteby, L. E. Studies on erythro-kinetics in infancy. VIII. Mixing, disappearance rates and distribution volume of labelled erythrocytes and plasma proteins in early infancy. *Acta Soc Med Upsal*, 72: 49. 1967

7 Braunitzer, G. The molecular weight of human haemoglobin. *Bibl Haemat*, 18: 59. 1964.

8 Brown, A. K. Neonatal jaundice. *Pediat Clin N Amer*. 9: 575, 1962.

9 Clark, R. T. Evidence for conversion of carbon monoxide to carbon dioxide by the intact animal. *Amer J Physiol*, 162: 560, 1950.

10 Coburn, R. F. Endogenous carbon monoxide production and body CO stores. *Acta Med Scand, Suppl 472*. 269. 1967

11 Coburn, R. F. Blakemore, W. S. and Forster, R. E. Endogenous carbon monoxide production in man. *J Clin Invest*. 42: 1172, 1963.

12 Coburn, R. F. Forster, R. E. and Kane, P. B.. Considerations of the physiological variables that determine the blood carboxyhaemoglobin concentration in man. *J Clin Invest*, 44: 1899. 1965.

13 Coburn, R. F. Williams, W. J. and Forster, R. E. Effect of erythrocyte destruction on carbon monoxide production in man. *J Clin Invest*. 43: 1098. 1964.

14 Coburn, R. F. Williams, W. J. and Kahn, S. B. Endogenous carbon monoxide production in patients with hemolytic anemias. *J Clin Invest*. 45: 460, 1966.

15 Collison, H. A., Rodkey, F. L. and O'Neal, J. D.: Determination of carbon monoxide in blood by gas chromatography. *Clin Chem*, 14: 16., 1968.

16 Danks, D. M., Campbell, P. E. and Connelly, J. F. An aetiological study of neonatal jaundice in children's hospital. *Aust Paediat J*. 1: 193, 1965.

surpass the effect of the endogenous CO formation considerably Systematic determinations of the CO concentration in room air in the Children's hospital and the Obstetric Department indicated that the average contribution made by exogenous CO to the COHb level was comparatively small approximately amounting to 15-20 per cent of the normal mean level Similar determinations should be done in each hospital where COHb is used in the study of haemolytic diseases and should be repeated from time to time If the CO content in the ambient air is high and variable it can be determined together with the COHb and accounted for

Smokers often have COHb levels far in excess of those found in haemolytic disease Patients should not be allowed to smoke during 1-2 days preceeding an investigation With regard to the efficient CO elimination found from the first day after birth the COHb level can be used as an index of haemolysis after 1-2 days in an infant whose mother is a smoker

Coburn *et al* stressed the effect of the pulmonary CO elimination on the relation between the COHb level and the endogenous CO production and estimated that possible variations in ventilation and diffusing capacity should influence this relationship considerably [12] The present investigation indicated that in newborn infants without signs of pulmonary disease the influence of these factors was less varying. A close correlation was found between COHb and CO elimination per kg body weight ($r = 0.91$) In a steady state the COHb level thus can be assumed to give accurate information about the endogenous CO formation If the CO production increases the COHb level and the CO elimination will rise rapidly and a new steady state is probably reached within a few hours In the case of decreasing CO production the time lag in the CO elimination delays the new equilibrium by about 24 hours

It has been shown that fetal blood has an increased affinity for oxygen when compared with that of the adult [3]. This phenomenon was long assumed to be caused by the fetal haemoglobin but recent investigations indicate that the high affinity does not depend on the fetal haemoglobin *per se* but is a property of the red cells [3] The affinity for oxygen influences the equilibrium described by Haldane's equation In this context the affinity of fetal blood for carbon monoxide is also of importance Available information on this subject is scanty Engel *et al* have recently reported that fetal haemoglobin has a lower affinity for CO than adult haemoglobin [17], but did not give the difference or describe their experimental procedure These properties of the fetal blood can be assumed to reduce the numerical value of the constant in Haldane's equation Direct determination of the constant in fetal blood is, however necessary for the estimation of the effect on the COHb level. In this presentation the possible difference between fetal and adult blood has therefore been disregarded

The present investigation has shown that the indirect estimation of the endogenous CO formation from the CO saturation of blood is of value in the study of haemolytic diseases and of the pathogenesis of jaundice in newborn infants. A comparison of groups of patients should disclose even moderate differences in the rate of haemoglobin catabolism especially if the groups are examined under the same environmental conditions. In the individual the COHb level reveals an increased haemolysis in the majority of cases. The COHb level also allows a quantification of the rate of haemolysis, but the random error of an estimate of haemolysis from COHb seems to be relatively large.

SUMMARY

Carbon monoxide is a normal metabolite of the haemoproteins and the endogenous formation of CO mainly reflects the haemoglobin catabolism. The endogenous CO production was studied in newborn infants indirectly by determination of the CO saturation of blood

50 Oski, F. A. and Altman, A. A., Carboxyhaemoglobin levels in haemolytic disease of the newborn. *J Pediat*, *61* 709, 1962.

51 Palma Carlos, A. G., Palma Carlos, M.-L. and Dacha Soares, A., Formation endogène d'oxyde de carbone et catabolisme hémoglobinique. *Nouv Rev Franc Hemat*, *6* 225, 1966.

52 Robinson, S. H., Erythropoietic component of early-labeled bilirubin: role of "ineffective reticulocytosis" *Clin Res*, *16* 312, 1968.

53 Root, W. S., Carbon monoxide, in W. O. Fenn and H. Rahn (ed.): *Handbook of Physiology Section 3, Respiration II*. American Physiological Society Washington, D.C. 1964 p. 1087

54 Root, W. S. and Allen, T. H., Determination of red cell volume with carbon monoxide. *Meth Med Res*, *8*: 80, 1960.

55 Roughton, F. J. W. and Root, W. S., The fate of CO in the body during recovery from mild carbon monoxide poisoning in man. *Amer J Physiol*, *145* 239, 1945.

56 Schellong, G., *Ikterus neonatorum*. G. Thieme Verlag, Stuttgart 1961

57 Seip, M., The reticulocyte level and the erythrocyte production judged from reticulocyte studies in newborn infants during the first week of life. *Acta Paediat Scand*, *44*: 355, 1955.

58 Sendroy Jr. J., Liu, S. H. and van Slyke, D. D. The gasometric estimation of the relative affinity constant for carbon monoxide and oxygen in whole blood at 38°. *Amer J Physiol*, *90*: 511 1929

59 Sjöstrand, S. M. and Sjöstrand, T. A method for determination of low concentrations of carbon monoxide in the blood and the relation between the CO-concentration in the blood and that in the alveolar air. *Acta Physiol Scand*, *22* 129 1951

60 Sjolin, S. The resistance of red cells in vitro. *Acta Paediat Scand*, *Suppl 98* 1954

61 Sjöstrand, T. A method for the determination of carboxyhaemoglobin concentrations by analysis of the alveolar air. *Acta Physiol Scand*, *16* 201 1948.

62 Sjöstrand, T. A method for the determination of the total haemoglobin content of the body. *Acta Physiol Scand*, *16* 211 1948.

63 Sjöstrand, T. Endogenous formation of carbon monoxide in man under normal and pathological conditions. *Scand J Clin Lab Invest* *1* 201 1949

64 Sjostrand, T. Endogenous formation of carbon monoxide. The CO concentration in the inspired and expired air of hospital patients. *Acta Physiol Scand*, *22*: 137 1951.

65 Sjostrand, T. The in vitro formation of carbon monoxide in blood. *Acta Physiol Scand*, *24*: 314 1951.

66 Sjostrand, T., The formation of carbon monoxide by in vitro decomposition of haemoglobin in bile pigments. *Acta Physiol Scand*, *26* 328, 1952.

67 Sjostrand, T. Formation of carbon monoxide by coupled oxidation of myoglobin with ascorbic acid. *Acta Physiol Scand*, *26* 334, 1952.

68 Sjöstrand, T. The formation of carbon monoxide by the decomposition of haemoglobin in vivo. *Acta Physiol Scand*, *26* 338, 1952.

69 Somerville, P. N. Tables for obtaining non-parametric tolerance limits. *Annals of Mathematical Statistics*, *29*: 599, 1958.

70 Theorell, H., Beznac, M., Bonnichsen, R., Paul, K. G. and Åkeson, Å. On the distribution of injected radioactive iron in guinea pigs and its rate of appearance in some haemoproteins and ferritins. *Acta Chem Scand*, *5* 445, 1951

71 Vest, M. F. Studies on haemoglobin breakdown and incorporation of [^{15}N] glycine into haem and bile pigment in the newborn, in I. A. D. Bouchier and B. Billing (ed.) *Bilirubin metabolism*. Blackwell Scientific Publications, Oxford and Edinburgh 1967 p. 47

72 Vest, M. F. and Grieder H. R. Erythrocyte survival in the newborn infant, as measured by chromium[51] and its relation to the postnatal serum bilirubin level. *J Pediat*, *59*: 194, 1961

73 White, P. Coburn, R. F. Williams, W. J. Goldwein, M. I., Rother M. L. and Shafer B. C. Carbon monoxide production associated with ineffective erythropoiesis. *Blood*, *24* 845 1964.

74 White, P. Shafer B. C., Rother M. L. and Williams, W. J. Production of carbon monoxide by bone marrow and reticulocytes in vitro. *J Clin Invest* *47* 102a, 1968.

75 White, P. Silvers, A. A., Rother M. L., Shafer B. C. and Williams, W. J. Hepatic production of bilirubin and carbon monoxide in vitro. *J Clin Invest* *45* 1085 1966.

76 Wranne, L. Studies on erythro-kinetics in infancy VI. A method for the quantitative estimation of pulmonary excretion of carbon monoxide in infancy. *Acta Paediat Scand*, *56*: 374, 1967

77 Wranne, L. Studies on erythro-kinetics in infancy VII. Quantitative estimation of the haemoglobin catabolism by carbon monoxide technique in young infants. *Acta Paediat Scand*, *56* 381 1967

78 Yamamoto, T. Skanderberg, J. Zipursky A. and Israels, L. G. The early appearing bilirubin. Evidence for two components. *J Clin Invest* *44* 31 1965.

79 Zipursky A. The erythrocytes of the newborn infant. *Seminars Hemat* *2*: 167 1965

80 Zuelzer W. W. and Kaplan, E. ABO heterospecific pregnancy and hemolytic disease. A study of normal and pathologic variants. IV Pathologic variants. *Amer J Dis Child*, *88*: 319 1954.

17 Engel, R R Rodkey F L and Krill C E Detecting hemolytic states from carboxyhemoglobin levels. *Ped Res* 2 313 1968
18 Engstedt, L Endogenous formation of carbon monoxide in hemolytic disease. *Acta Med Scand Suppl 332* 1957
19 Forster R E Diffusion of gases, *in* W O Fenn and H. Rahn (ed) *Handbook of Physiology Section 3 Respiration I* American Physiological Society Washington D C 1964 p. 839
20 Freda, V J and Carter B A. Placental permeability in the human for anti A and anti B isoantibodies. *Amer J Obst Gyn 84* 1351 1962.
21 Furuhjelm, U Nevanlinna, H R and Österlund, K. Early neonatal jaundice and hyperbilirubinaemia and their relation to ABO incompatibility *Acta Paediat Scand 56* 477 1967
22 Gaensler E A. Cadigan Jr J B. Ellicott, M F Jones, R. H. and Marks, A A new method for rapid precise determination of carbon monoxide in blood. *J Lab Clin Med 49* 945 1957
23 Garby L, Sjolin S. and Vuille J-C. Studies on erythro-kinetics in infancy V Estimations of the life span of red cells in the newborn. *Acta Paediat Scand 53* 165 1964
24 Gemzell, C. A Robbe, H and Strom, G On the equilibration of carbon monoxide between human maternal and fetal circulation *in vivo* *Scand J Clin Lab Invest 10* 372, 1958.
25 Gray C H Neuberger A. and Sneath P H A. Studies in congenital porphyria. 2 Incorporation of N in the stercobilin in the normal and in the porphyric. *Biochem J 47* 87 1950.
26 Gray C. H Nicholson, D C and Nicolaus, R A. The IX *α* structure of the common bile pigments. *Nature 181* 183 1958.
27 Gréhant, N *Les gaz du sang* G Masson, Paris 1894
28 Grundbacher F J Quantitative variation of the A antigen at birth Its significance in ABO hemolytic disease and in the infant s development *Acta Paediat Scand 54* 550 1965
29 Gydell, K. Transient effect of nicotinic acid on bilirubin metabolism and formation of carbon monoxide *Acta Med Scand, 167* 431 1960
30 Halbrecht, J Role of hemoagglutinins anti A and anti-B in the pathogenesis of jaundice of the new born (icterus neonatorum precox). *Amer J Dis Child 68* 218 1944
31 Hallberg, L. Blood volume haemolysis and regeneration of blood in pernicious anaemia. *Scand J Clin Lab Invest Suppl 16*, 1955
32 Hodgman, C O and Holmes, H. N *Handbook of Chemistry and Physics.* Chemical Rubber Publishing Co Cleveland 1942.
33 Holt, Jr L. E. McIntosh, R. and Barnett, H. L. Growth and development, *in* L. E. Holt Jr R. McIntosh and H L. Barnett (ed.) *Pediatrics.* Appleton-Century-Crofts, Inc, New York 1962, p. 1
34 Jendrassik, L. and Cleghorn R. A. Photometrische Bilirubinbestimmung. *Biochem Z 289* 1 1936.
35 Jendrassik L. and Gróf P Vereinfachte photometrische Methoden zur Bestimmung des Blut bilirubins. *Biochem Z 297* 81 1938.
36 Kalpaktsoglou, P K and Emery J L The effect of birth on the haemopoietic tissue of the human bone marrow *Brit J Haemat 11* 453 1965
37 Koch, G Lung function and acid-base balance in the newborn infant. *Acta Paediat Scand, Suppl 181* 1968
38 Kochwa S., Rosenfield, R E. Tallal L and Wasserman, L R Isoagglutinins associated with ABO erythroblastosis. *J Clin Invest 40* 874 1961
39 Künzer W Der Ikterus des Neugeborenen. Ein Überblick Teil II Ikterusformen des Neugeborenen. *Ann Paediat 198* 314 1962.
40 Linderholm H and Sjostrand, T Determination of carbon monoxide in small gas volumes. *Acta Physiol Scand, 37* 40 1956.
41 Linderholm, H Sjostrand T and Soderstrom, B. A method for determination of low carbon monoxide concentration in blood. *Acta Physiol Scand 66* 1 1966.
42 London, I M. West R Shemin, D and Rittenberg, D On the origin of bile pigment in normal man. *J Biol Chem 184* 351 1950.
43 Loumanmaki, K Studies on the metabolism of carbon monoxide *Ann Med Exp Fenn Suppl 2* 1966.
44 Mollison, P L The survival of transfused erythrocytes in haemolytic disease of the newborn. *Arch Dis Child 18* 161 1943
45 Nakajima, H Takemura, T Nakajima, O and Yamaoka, K. Studies on heme α-methenyl oxygenase I The enzymatic conversion of pyridine-hemichromogen and hemoglobin-haptoglobin into a possible precursor of biliverdin. *J Biol Chem 238* 3784 1963
46 Nelson, T C The relationship between melena and hyperbilirubinemia in mature neonates. *Biol Neonat 8* 267 1965
47 Nicloux, M Sur l oxyde de carbone contenu normalement dans le sang *C R Acad Sci [D] (Paris), 126* 1526 1898
48 Nilsson, S. B. *Maternal A and B antibodies in ABO haemolytic disease of the newborn.* Sydsvenska Dagbladets AB, Malmo 1967
49 Nomof N Hopper Jr J Brown, E Scott, K. and Wennesland, R Simultaneous determinations of the total volume of red blood cells by use of carbon monoxide and chromium in healthy and diseased human subjects. *J Clin Invest 33* 1382, 1954

50 Oski, F. A. and Altman, A. A., Carboxyhaemoglobin levels in haemolytic disease of the newborn. *J Pediat 61*: 709, 1962.

51 Palma Carlos, A. G., Palma Carlos, M.-L. and Dodo Soares, A., Formation endogène d'oxyde de carbone et catabolisme hémoglobinique. *Nouv Rev Franc Hémat 6*, 225, 1966.

52 Robinson, S. H., Erythropoetic component of early-labeled bilirubin: role of "ineffective reticulocytosis". *Clin Res, 16* 312, 1968.

53 Root, W. S. Carbon monoxide, *in* W. O. Fenn and H. Rahn (ed.): *Handbook of Physiology. Section 3 Respiration II.* American Physiological Society Washington, D.C. 1964, p. 1087

54 Root, W. S. and Allen, T. H. Determination of red cell volume with carbon monoxide. *Meth Med Res, 8*: 80, 1960.

55 Roughton, F. J. W. and Root, W. S. The fate of CO in the body during recovery from mild carbon monoxide poisoning in man. *Amer J Physiol, 145* 239, 1945.

56 Schellong, G., *Hæmes neonatorum.* G. Thieme Verlag, Stuttgart 1961

57 Seip, M. The reticulocyte level and the erythrocyte production judged from reticulocyte studies in newborn infants during the first week of life. *Acta Paediat Scand, 44* 355, 1955

58 Sendroy Jr J. Liu, S. H. and van Slyke, D. D., The geometric estimation of the relative affinity constant for carbon monoxide and oxygen in whole blood at 38. *Amer J Physiol, 90*: 511 1929

59 Sonnem, S. M. and Sjostrand, T. A method for determination of low concentrations of carbon monoxide in the blood and the relation between the CO-concentration in the blood and that in the alveolar air. *Acta Physiol Scand, 22* 129 1951

60 Sjolin, S. The resistance of red cells *in vitro*. *Acta Paediat Scand, Suppl 98* 1954

61 Sjöstrand, T. A method for the determination of carboxyhaemoglobin concentrations by analysis of the alveolar air. *Acta Physiol Scand, 16* 201 1948.

62 Sjöstrand, T. A method for the determination of the total haemoglobin content of the body. *Acta Physiol Scand, 16* 211 1948

63 Sjostrand, T. Endogenous formation of carbon monoxide in man under normal and pathological conditions. *Scand J Clin Lab Invest 1* 201 1949

64 Sjöstrand, T. Endogenous formation of carbon monoxide. The CO concentration in the inspired and expired air of hospital patients. *Acta Physiol Scand, 22*: 137 1951

65 Sjöstrand, T. The *in vitro* formation of carbon monoxide in blood. *Acta Physiol Scand, 24* 314, 1951.

66 Sjöstrand, T., The formation of carbon monoxide by *in vitro* decomposition of haemoglobin in bile pigments. *Acta Physiol Scand, 26* 328, 1952.

67 Sjostrand, T., Formation of carbon monoxide by coupled oxidation of myoglobin with ascorbic acid. *Acta Physiol Scand, 26* 334 1952.

68 Sjöstrand, T. The formation of carbon monoxide by the decomposition of haemoglobin *in vivo*. *Acta Physiol Scand, 26* 338, 1952.

69 Somerville, P. N. Tables for obtaining non-parametric tolerance limits. *Annals of Mathematical Statistics, 29*: 599, 1958.

70 Theorell, H., Beznac, M., Bonnichsen, R., Paul, K. G. and Åkeson, Å., On the distribution of injected radioactive iron in guinea pigs and its rate of appearance in some haemoproteins and ferritins. *Acta Chem Scand, 5* 445 1951

71 Vest, M. F. Studies on haemoglobin breakdown and incorporation of [N] glycine into haem and bile pigment in the newborn, *in* L. A. D. Bouchier and B. Billing (ed.) *Bilirubin metabolism.* Blackwell Scientific Publications, Oxford and Edinburgh 1967 p. 47

72 Vest, M. F. and Grieder H. R. Erythrocyte survival in the newborn infant, as measured by chromium and its relation to the postnatal serum bilirubin level. *J Pediat 59*: 194, 1961

73 White, P. Coburn, R. F. Williams, W. J. Goldwein, M. I. Rother, M. L. and Shafer, B. C. Carbon monoxide production associated with ineffective erythropoiesis. *Blood, 4* 845, 1964.

74 White, P. Shafer, B. C., Rother, M. L. and Williams, W. J. Production of carbon monoxide by bone marrow and reticulocytes *in vitro*. *J Clin Invest 47* 102a, 1968.

75 White, P. Silvers, A. A., Rother, M. L., Shafer, B. C. and Williams, W. J. Hepatic production of bilirubin and carbon monoxide *in vitro*. *J Clin Invest 45* 1083, 1966

76 Wranne, L. Studies on erythro-kinetics in infancy VI. A method for the quantitative estimation of pulmonary excretion of carbon monoxide in infancy. *Acta Paediat Scand, 56*, 374, 1967

77 Wranne, L. Studies on erythro-kinetics in infancy VII. Quantitative estimation of the haemoglobin catabolism by carbon monoxide technique in young infants. *Acta Paediat Scand, 56* 381 1967

78 Yamamoto, T. Skanderberg, J. Zipursky, A. and Israels, L. G. The early appearing bilirubin. Evidence for two components. *J Clin Invest 44* 31 1965.

79 Zipursky, A. The erythrocytes of the newborn infant. *Seminars Hemat, 2*: 167 1965

80 Zuelzer, W. W. and Kaplan, E., ABO heterospecific pregnancy and hemolytic disease. A study of normal and pathologic variants. IV. Pathologic variants. *Amer J Dis Child, 88*: 319 1954



List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

131 Mellbin, Tore The Children of Swedish Nomad Lapps. A Study of their Health, Growth and Development. Sw. kr 25.— 1962
132. Börjeson, Mats, Overweight Children. Sw kr 25.— 1962
133. Lundström, Rolf, Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella. Sw kr 25.— 1962
134. Müller Tage, Shunt Operations in Morbus Caeruleus. Results in 161 Cases and Clinical Follow-up. Sw. kr 25.— 1962
135. *In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet*, June 30, 1962. Sw kr 25.— 1962
136. Bille, Bo, Migraine in School Children. A study of the incidence and short-term prognosis, and clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Sw. kr 25.— 1962
137 Hansen, A. E. Stewart, R. A., Hughes, G. and Söderhjelm, L., The Relation of Linoleic Acid to Infant Feeding. A Review. Sw. kr 25.— 1962
138. Wallgren, Erik Ivar, Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus, Pre- and Postoperative Studies of Thirty-four Cases. Sw kr. 25.— 1962
139. Westin, Björn, Nyberg, Rune, Miller James A., Jr. and Wedenberg, Erik, Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum. Sw. kr 30.— 1962
140. *The Proceedings of the Thirteenth Northern Paediatric Congress.* Copenhagen. 1961. Edited by E. Winge Flensborg. Sw. kr 30.— 1963
141 Waaz-Höckert, Ole and Donner Märta, Late Prognosis in Tuberculous Meningitis. A clinical, neurological, ophthalmological, otological, psychological, psychiatric, electroencephalographical, radiological and sociomedical study Sw. kr 25.— 1963
142. Sterner Göran, Adenovirus Infection in Childhood. An epidemiological and clinical survey among Swedish children. Sw. kr 25.— 1963
143. Lundberg, Åke, Paroxysmal Tachycardia in Infancy. A Clinical and Experimental Study. Sw kr 25.— 1963
144. Sterky Göran, Diabetic Schoolchildren. Sw. kr 30.— 1963
145. Walsh, S. Zoe, Evolution of the Electrocardiogram of Healthy Premature Infants During the First Year of Life. Sw. kr. 20.— 1963
146. *In Honour of Sture Siwe at his Retirement from the Professorship of Paediatrics at the University of Lund, June 30, 1963.* Sw. kr 25.— 1963
147 Åstrand, P.-O., Engström, L., Eriksson, B. O., Karlberg, P Nylander I., Saltin, B. and Thorén, C., Girl Swimmers. With Special Reference to Respiratory and Circulatory Adaptation and Gynaecological and Psychiatric Aspects. Sw kr 25.— 1963
148. Berven, Hans, The Physical Working Capacity of Healthy Children, Seasonal Variations and Effect of Ultraviolet Irradiation and Vitamin-D Supply. Sw. kr 20.— 1963
149 Valaes, Tamas, Bilirubin Distribution and Dynamics of Bilirubin Removal by Exchange Transfusion. Sw kr 25.— 1963
150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw kr. 25.— 1963
151 *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw kr 15.— 1963
152. Hjern, Bo and Nylander Ingvar Acute Head Injuries in Children Traumatology Therapy and Prognosis. Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw kr 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study Sw. kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics*. Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr 25.— 1964
157 Brante G., Kaijser, K. and Öckerman, P A., Glycogenosis Type 1 (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm. 1964. Edited by Y. Larsson, Sw. kr. 25.— 1965
160. Öckerman, P A., Glycogen Storage Disease in Sweden. Sw. kr 25.— 1965
161. Peltonen, T and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr 25.— 1966
163. *Newborn Infant Cry* Edited by John Lind, Sw. kr 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis. A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr 35.— 1966
167 Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw kr 30.— 1966
168. Trojaborg, W Focal Spike Discharges in Children, Longitudinal Study Sw. kr 25.— 1966
169 Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171 Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A Morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Choremis.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hänninen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177 *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967 Sw. kr 35.— 1967
178. Kjägren Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179 *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Günter Lung Function and Acid-Base Balance in the Newborn Infant. Sw kr 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study Sw kr 25.— 1968
183. Robertson, Alex F and Sprecher Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr 25.— 1968
185. Andersen, Elsa, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw kr 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw kr. 25 — 1968
187 Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community A Prospective Longitudinal Study I–VI. Sw kr 30.— 1969
188. Meeuwisse, Gunnar W and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 cases and Genetic Study Sw kr 25.— 1969
189 Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw kr 20.— 1969

Price Swed. kr 20 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ut697

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 188 1969

STUDIES IN GLUCOSE GALACTOSE MALABSORPTION

A CLINICAL STUDY OF 6 CASES AND A GENETIC STUDY

BY GUNNAR W MEEUWISSE AND KERSTIN MELIN

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 188, 1969

STUDIES IN GLUCOSE-GALACTOSE MALABSORPTION

A CLINICAL STUDY OF 6 CASES AND A GENETIC STUDY

by

Gunnar W Meeuwisse and Kerstin Melin

UPPSALA 1969

PRINTED IN SWEDEN BY
Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1969

Acta Pædiat Scand Suppl 188 1969

GLUCOSE-GALACTOSE MALABSORPTION

A Clinical Study of 6 Cases

G. W. MEEUWISSE and K. MELIN

Department of Pediatrics, University of Lund, Sweden, and Department of Pediatrics, University of Umeå, Sweden

In a previous article (28) a case of monosaccharide malabsorption was described. Two more cases were mentioned by us in a preliminary report (31) in which the name of this condition was altered to the more adequate, glucose-galactose malabsorption (GGM). The present paper reports the clinical data of six patients, all being inhabitants of a rather circumscribed area in Northern Sweden. One more case has been found in another part of Sweden (21). Now it is clear however that the condition is not confined to this country. Simultaneously with our first study a group of French investigators observed two cases of what they termed "Intolerance to actively transported sugars" which is evidently the same disease (25). More recently the disorder has been described in other countries (1 3 12, 33–35 48)

CLINICAL PICTURE

Case histories

The clinical material consisted of 6 cases of GGM. Four children without gastro-intestinal disorders and in good health served as controls for galactose TTs. The individual case histories of the patients with GGM are reported below. Some clinical data are, however presented in Table 1. Pregnancies and births were uneventful for all cases except Case 5 born 2 weeks after term, and Case 6, born with the aid of a vacuum extractor. Routine laboratory findings obtained soon after admission are listed in Table 2. The results of some simple tests on the absorption and excretion of carbohydrates are summarized in Table 3

Case 1

A girl, born on October 13 1958, was admitted at 9 days of age due to diarrhoea from her 3rd and vomiting from her 7th day of life.

History before admission. Breast milk and additional cow milk was given for the first four days of life. Subsequently only high casein formula containing sucrose and lactose was given. The frequent stools kept their watery consistency

On admission, weighing 300 g less than at birth, her general condition was good. Spontaneous motility was lively and she ate with a good appetite. She had a vigorous cry. Physical examination: nil, except a moderate decrease of turgor

Serum chloride was high. The low serum sodium content was probably erroneously measured (Table 2). Acidosis was present. There was slight proteinuria and a positive Clinitest test. Later on the proteinuria disappeared but the glucosuria persisted. The urinary sediment was normal.

Course in the hospital. Diarrhoea and vomiting continued on feeding with equal amounts of breast milk and tea containing 5 per cent glucose. After 2 days a soy flour formula with sucrose as the main

---

Abbreviations: GGM, glucose-galactose malabsorption; GTT glucose tolerance test; PEG, polyethylene glycol, TRIS, trihydroxymethyl aminomethane; TT tolerance test (with oral load of sugar other than glucose).

Table 1 *Main clinical data in six cases with glucose-galactose malabsorption*

Case nr	Present age	Age at first hospitalization (days)	Diet before admission	Age at onset of diarrhoea (days)	Birth weight (g)	Weight at admission (g)	Fever (above 38°C)	Vomiting	Diet resulting in amelioration	Additional disorders
1	9 ys	9	Breast milk and a formula with sucrose	3	3650	3150	+	+	Mullsoy Sobee	Renal concrements
2	† 2 mos	50	Breast milk and a formula with sucrose	"few"	3500	2790	–	+	–	Candida infection of mouth. Nephrocalcinosis.
3	4½ ys	9	Breast milk	1	4000	?	?	–	Formula with water milk, oats, sucrose (Mullsoy)	Renal concrements
4	7 ys	5	Breast milk	4	3370	2600	+	–	Fructose formula	
5	† 3 mos	5	Breast milk	4	3600	3100	–	–	Fructose formula	Candida infection of mouth. Hypogammaglobulinemia. Pulmonary disease. Myocarditis. Staphylococcus dermatitis
6	6 ys	4	Breast milk	2	4100	3500	+	–	Fructose formula	

† Deceased

carbohydrate (Mullsoy®) was given. The symptoms ceased and she started to gain in weight but the increments soon diminished. Additional glucose solutions exceeding a concentration of 3 per cent resulted in loose stools.

During this period, while the patient was in reasonable balance, the serum electrolyte, acid-base balance, serum protein, haematocrit and NPN values were normal. The fasting blood sugar varied between 70 and 110 mg/100 ml as measured by a reduction method (16). GTT and galactose TT resulted in flat curves. After the galactose TT increased diarrhoea was observed, and small amounts of urinary glucose were found whereas urinary galactose was absent.

At 3 months, when her weight was 4000 g breast milk feeding was retried. Again frequent stools resembling urine resulted and she became severely dehydrated. A slight fever was observed. Acidosis and dehydration were more pronounced than at admission (cf Table 2): HCO_3 5 mEq/l, Na 149 mEq/l, NPN 63 mg/100 ml and protein 6.7 g/100 ml. The paper electrophorogram was normal. The Clinistix test on the watery stools was strongly positive whereas it was negative on urine. She received glucose and electrolytes intravenously; orally she was given small amounts of breast milk, and tea containing 5 per cent fructose. The latter monosaccharide was chosen because empirically glucose had been found to be harmful in this case. Several formulae were then tried to no benefit. Finally a soy flour formula (Sobee®), containing corn sugar and sucrose, was given again. From that time (6 months) she gained weight steadily and the stools became semisolid. Other foods were introduced, fish, meat, eggs. Most fruit juices and vegetables were well tolerated, while grape juice, winter carrots and starch gave diarrhoea. At times glucosuria was found with the Clinistix test with no correlation with the clinical state. When the patient was dismissed from the hospital at the age of 8 months, she weighed 6490 g and her psychomotor development was normal.

History after discharge. The further course has been characterized by short periods of diarrhoea especially after ingestion of milk and starch-rich foods. An attack of pyelitis occurred at 3 years and she was again given hospital treatment. The intravenous pyelogram revealed stones in the left ureter and a left-sided hydronephrosis. Upon reinspection of an abdominal X-ray made when she was 4 months old, small renal concrements were visible. Four stones were removed by surgery, one of the stones contained calcium oxalate and the others calcium phosphate. Urinary excretion of calcium and phosphorus was normal. Endogenous creatine clearance was 1.4 ml/min/1.73 sq.m and maximal specific gravity of the urine after pitressin administration was 1025. Renal acidifying capacity (53) was tested at 6 years of age and found to be impaired, the lowest pH after ammonium chloride administration being 5.6.

At several check-ups her mental and physical development was found to be normal (8 years, weight 20.3 kg and height 120 cm). *Her diet is restricted in*

Table 2. *Various laboratory findings soon after admission in five cases with glucose-galactose malabsorption.*

Case nr	Serum electrolytes, (mEq/l)				NPN (mg/100 ml)	Serum Protein (g/100 ml)	Hb (g/100 ml)	RBC 10^6	WBC (cells/mm³)
	Na	K	Cl	HCO_3					
1	134	5.8	120	12	53	6.2	21.5	6.0	18,400
2	166	4.2	—	—	—	—	13.2	4.1	7,900
4	160	5.3	130	16	50	7.5	19.6	6.0	11,300
5	—	—	—	—	—	7.4	18.3	5.1	17,200
6	173	5.8	120	9.5	78	7.6	20.2	6.8	13,900

Serum creatine was 1.1 mg/100 ml.

milk and starch-containing foods and, for sweetening, fructose is used in place of sucrose.

Case 2

A girl, born on January 26, 1957 an elder sister of Case 1 was admitted at 7 weeks of age because of diarrhoea and vomiting from her 4–5th day

History before admission. Owing to continuous diarrhoea, whereby she lost 400 g in weight during the first week of life, breast feeding was stopped at about 2 eeks of age and instead different cow's milk formulae containing sucrose and wheat flour or corn starch were tried. Tea with glucose was also given ithout amelioration of the diarrhoea or the vomiting. She continued to lose weight.

O admission her general condition was severe. She had the appearance of a chronically ill and severely malnourished child. She had no fever. The *pulse rate was 155/min.* The skin was pale *and* dry with a decreased turgor. Besides thrush stomatitis she had a sore throat and physical signs of bronchitis. The abdomen was meteoristic. The chest X-ray was normal whereas the abdominal X-ray showed distended, gas filled loops with no signs of obstruction. The ECG was normal. Slight albuminuria and leucocyturia were demonstrated and the urine also contained reducing substance as measured by Almén method (2, 41). Serum sodium was increased (Table 2).

Course in the hospital. She was treated with intravenous glucose and electrolytes and, in addition, penicillin and blood transfusions. The diet was altered to breast milk, *given in small amounts. The following day* her general condition was slightly improved de spite continued watery diarrhoea and occasional vomiting. On the third day after admission she suddenly became worse *with impaired* breathing and somnolence, and died soon after

Autopsy revealed moderately distended small-intestine loops, containing watery *yellow non-offensive*, sour-smelling fluid. The same fluid was present in the proximal colon, and *distally* some semisolid greenish material was found. There were no signs of enteritis. Cultures *revealed* non-pathogenic *E. Coli* and Enterococcus. The liver was considered to be slightly enlarged and somewhat pale. The bile tract was normal as was the pancreas. Gross anatomy of the kidneys was normal with the exception of several ery pale, small areas within the papillary region. At microscopy these areas were found to contain crystalline material within the distal tubules and adjacent interspaces (nephrocalcinosis). The posterior basal *segments of the lungs* were atelectatic; microscopically the distal airways contained an exudation of leukocytes. The heart was normal. The brain showed no significant abnormalities. The immediate cause of death could not be established.

Case 3

A woman, born on October 2, 1926 was discovered to be case of *GGM when the heredity of* Case 1 and 2 was penetrated: she was distantly related to them.

History before (actual) admission. Being breastfed, watery diarrhoea began *immediately. At 9 days of age she was admitted to* cottage *hospital, where a* buttermilk formula and whole milk formula were tried without any improvement. Since the baby's condition became worse, she as taken home and her mother made a formula of water small amounts of cow's milk, oats and sucrose. *Given this the baby* began to gain in weight for the first time and at 4 months she weighed 5800 g. From 6 months of age she also ate fish, meat and eggs mixed with cream and water. She slowly increased in weight but during infancy she always had loose stools *and* a large abdomen. At one year *of age she* was seen by the local practitioner. *His diagnosis* was celiac disease and he forbad milk and cereals. Later during childhood she maintained tendency towards loose stools, and was often abnormally thirsty. Menarche occurred at 20 years.

I adulthood she still has digesti problems. More than ha-f glass of milk results in abdominal cramp and loose stools. Bread, pancakes and more than one potato give the same symptoms. Some fruit such as bananas, apples and oranges also cause abdominal cramps. On *diet chiefly consisting of fish*, meat, cream, butter *oat* porridge and not more than one slice *of bread per meal* she is symptom-free.

— 680343 Mattsson

Since the age of 10 she experienced low back pain. There is no evidence of osteoporosis on X-ray examinations. At the age of 12 the patient had epidemic hepatitis without sequelae. At 32 years she was operated for toxic struma and then renal glucosuria was noted for the first time. GTT's were flat.

On admission she was 36 years old and in a good mental and physical state (body weight 66 kg height 177 cm). The diagnosis of GGM was confirmed by an intestinal intubation study which showed that glucose was absorbed more slowly than fructose (29). Results of studies on mucosal biopsy specimens have been published elsewhere (37).

History after discharge At 38 years of age the patient had colics during passage of small renal concrements. On a second occasion the stone was collected and analyzed, it contained calcium, ammonium, oxalate and phosphate. All concrements passed spontaneously. There were no other abnormalities at X-ray examination or on an intravenous pyelogram.

Case 4

A girl, born on September 7 1961 was admitted at 18 days of age owing to diarrhoea from her 4th day. The patient has previously been described in detail (28).

History before admission She was breastfed for one week. From her 5th day she was treated at the pediatric department of another hospital. Due to continuous diarrhoea with watery stools resembling urine, several formulae containing different sugar contents were tried instead. Parenteral fluid was also given.

On admission her general condition was good and there were no signs of dehydration. Spontaneous motility was lively and she had a good appetite. Serum electrolytes were increased and there was a moderate acidosis (Table 2). Clinistix reaction on urine was positive. Glucose was demonstrated in the feces.

Course in the hospital She improved on a soy flour formula with a low carbohydrate content (Mulsoy®). During the first half year she suffered frequent infections of the respiratory tract. The Clinistix reaction on the urine was sometimes weakly positive, sometimes negative. Different oral sugar loading tests were performed. The results of these, as well as of an intubation study leading to the diagnosis of glucose galactose malabsorption, have been published elsewhere (28).

When, at about 6 months of age, she was given a fructose formula (30) the stools immediately became normal. Solid foods were introduced at 7 months and the daily volume of the fructose formula could successively be reduced. She weighed 7000 g when discharged from the hospital at 9 months of age.

History after discharge This was rather uneventful. To avoid loose stools she had, however to be maintained on a diet with certain limitations regarding milk and starch-containing foods. Oats seemed to be better tolerated than other cereals. From the age of 1 year she ate fructose formula only once or twice a day At 2 years she could tolerate 1 glass of milk, 4 sandwiches and 2 potatoes a day spaced over several meals, without any trouble. When 5 / years old her height was 107 cm and weight 17 9 kg. Physical and mental development was perfectly normal. She tolerated 2 glasses of milk a day 3–4 sandwiches and 3 potatoes. All fruits except grapes could be eaten without adverse consequences.

Case 5

A boy born on March 30, 1964 a younger brother of Case 4, was admitted at 4 days of age because of diarrhoea noted from the 4th day

History before admission. He was born ? weeks after term and he had been breast fed. Due to severe diarrhoea, the stools resembling urine, he was transferred from the maternity hospital to the department of pediatrics.

On admission he weighed 500 g below his birth weight but his general condition was satisfactory. Spontaneous motility was lively and he had a good appetite. He had a moderate decrease of turgor. The presence of glucose in the stools and in the urine was demonstrated with the Clinistix test. Some other laboratory data are shown in Table 2.

Course in the hospital Breast feeding was stopped and the infant instead received a fructose formula (30). The stools immediately became normal and the patient began to gain in weight.

The GTT and galactose TT resulted in flat blood glucose curves, the fructose TT indicated a normal fructose absorption (Table 3 and 5)

History after discharge For the next few months the patient was well. At 3 months of age he acquired a stomatitis, which was unsuccessfully treated with Chloromycetin, and he was therefore readmitted to the hospital.

On (second) admission he had a severe *Candida* infection in his mouth. His general condition worsened successively and the *Candida* infection spread to the skin. Soon he showed signs of respiratory insufficiency and the chest X-ray revealed pulmonary infiltrations.

ESR was 21 and the WBC varied between 22,500 and 8000. The differential count was normal (lymphocytes 53 and 66 per cent on two occasions). The total serum protein was low (4 1 g/100 ml). The paper electrophorogram, which had been normal at 2 weeks of age, was pathological with a borderline low albumin value (3 1 g/100 ml) and a low gammaglobulin value (0 1 g/100 ml). The α 2-globulin was relatively elevated (0.4 g/100 ml), whereas the α 1 and the β-globulins were normal. The patient was found to have anti A and anti B isoagglutinins in his

---

After a modification with regard to salts this formula contains Calcium caseinate 2 3 %, corn oil 3.5 %, fructose 4–8 %, and furthermore, per liter formula 1 Tsp. of a salt mixture (KCl, NaCl, $CaHPO_4$, $2H_2O$ mixture 2 1 1 w/w), 1 Tabl. Minovit® (a multivitamin and trace mineral preparation) and 1/2–1 Tsp. Nestargel® for adjustment of consistency

serum. On the immunoelectrophoresis there was weak γ-G band, γ-A and γ-M could not be distinguished. The patient died rather suddenly after two weeks in the hospital; he was thought to have aspirated during coughing.

Autopsy. No signs of widespread *Candida* infection of the gut or respiratory tract were found. The basal parts of the lungs were atelectatic; microscopically there were atelectatic parts in other lung segments too. An unspecific inflammatory picture with giant cells was seen in the bronchi with surrounding parenchyma, no epitheloid cells were found, and no mycelia were visible with special staining. The histological picture resembled *Pneumocystis Carinii* infection, but this organism was absent in the specimens. The thymus was macroscopically normal and weighed 5 g. Microscopically there was a rather marked atrophy of the lymphoid component of this organ. Lymph nodes from different parts of the body showed lymphoid atrophy with very small and indistinct secondary follicles and few reaction centres. The spleen showed atrophic Malpighian corpuscles without reaction centres. The histological preparations of the bone marrow were difficult to interpret with respect to the presence of small lymphocytes or plasma cells. The small intestine was strongly autolytic. There were no lymph follicles.

Case 6

A boy born on May 24, 1962, was admitted at 4 days of age because of diarrhoea from his 2nd day and fever from his 3rd day of life.

History before admission. A vacuum extractor was used at the otherwise normal delivery. He was breastfed for one week. Due to watery diarrhoea he lost 600 g of his weight in 4 days. A temperature of 38.4°C was recorded at the maternity department.

On admission, his general condition was fairly good, although a moderate decrease of skin turgor was observed. Spontaneous motility was lively and he had a good appetite.

The Clinistix test on the feces was strongly positive. Nearly 6 g of sugar, 2.7 g of which was glucose, was found per 100 g wet feces. The Clinistix test on the urine was sometimes positive and sometimes negative. Albuminuria was observed during the first 2 days after admission. At the same time the urinary sediment contained a considerable quantity of red and white blood cells and abundant crystals, but a new sediment a few days later was found to be normal. It was doubtful if the urinary tract was infected; sulfonamides were, however given for a few days.

Course in the hospital. He continued to have profuse watery diarrhoea, and during the 4 days after admission he lost an additional 230 g in weight. By then he looked dehydrated and his motility decreased. The peripheral circulation seemed poor. Hyperelectrolytaemia and metabolic acidosis were found (Table 2). The ECG was normal. During rehydration with intravenously administered fluid he had convulsions for 25 minutes. He increased his weight by 460 g within two days.

Replacement of mother's milk by a fructose formula (30) was followed by diminished diarrhoea and a fall of the fecal sugar content to less than 0.03 per cent of wet weight. The diet was abandoned, however because of vomiting and weight loss.

When the baby was 2 weeks old, tachycardia and ventricular extrasystoles were observed and general adynamia occurred. Serum potassium was normal and there were no signs of hypokalemia on the ECG. Nevertheless, potassium chloride was given orally. The next day pulmonary congestion and a considerable enlargement of the heart was seen on X-ray. During the next few days the tachycardia increased and the liver became enlarged. Shifting ECG findings occurred with increased PR-interval, transient extrasystoles and negative T-waves over the left ventricle. The pulse rate and heart size gradually became normal during the following weeks. The clinical course of this complication was consistent with the diagnosis of infantile myocarditis. Virus isolation from the feces was negative and the serum did not contain neutralizing antibodies against Cox-Sackie B virus. Feces cultures showed a pathogenic strain of E. coli, and the patient was given broad spectrum antibiotics. In a few days he developed a widespread staphylococcal dermatitis in the face and the axillary regions. The feces now contained a dominating flora of *Staphylococcus aureus*.

The diet had been changed to a soy flour formula with a low carbohydrate content (Mulsoy ?) with extra amounts of water. Weight gain was slow and he had 2–3 semisolid stools a day. From 1 month of age limited amounts of the fructose formula were added without ill effects.

At the age of about two months a definite diagnosis of GGM was secured by oral sugar loading tests including a GTT and a galactose TT which resulted in flat blood sugar curves and increased fecal sugar. From that age the patient was consequently fed the fructose formula (30) after which the diarrhoea subsided. He was nearly 10 weeks old when he finally attained his birth weight again. Subsequently his growth was rapid and he gradually reached a normal weight in relation to his length. He was discharged at 6 months of age when his body weight was 6500 g.

History after discharge. The daily amounts of the fructose formula could be reduced as the amount of solid food was successively increased. At the age of 1 year he received about 200 g of the fructose formula twice a day. Otherwise he ate eggs, fish, meat, vegetables and fruit. He tolerated up to 300 ml of cream a day. He refused oat meal porridge which earlier he had tolerated in limited amounts. He also disliked potatoes. One slice of white bread resulted in diarrhoea.

Successive studies showed that the physical and mental development of this boy has been normal. At 3 1/2 years of age he was 112 cm tall and weighed 17 kg. His belly has a tendency to swell when he eats

Since the age of 10 she experienced low back pain. There is no evidence of osteoporosis on X-ray examinations. At the age of 12 the patient had epidemic hepatitis without sequelae. At 32 years she was operated for toxic struma and then renal glucosuria was noted for the first time. GTT's were flat.

On admission she was 36 years old and in a good mental and physical state (body weight 66 kg; height 177 cm) The diagnosis of GGM was confirmed by an intestinal intubation study which showed that glucose was absorbed more slowly than fructose (29) Results of studies on mucosal biopsy specimens have been published elsewhere (37).

History after discharge At 38 years of age the patient had colics during passage of small renal concrements. On a second occasion the stone was collected and analyzed, it contained calcium, ammonium, oxalate and phosphate. All concrements passed spontaneously There were no other abnormalities at X ray examination or on an intravenous pyelogram.

Case 4

A girl born on September 7 1961 was admitted at 18 days of age owing to diarrhoea from her 4th day The patient has previously been described in detail (28).

History before admission She was breastfed for one week. From her 5th day she was treated at the pediatric department of another hospital. Due to continuous diarrhoea with watery stools resembling urine, several formulae containing different sugar contents were tried instead. Parenteral fluid was also given.

On admission her general condition was good and there were no signs of dehydration. Spontaneous motility was lively and she had a good appetite. Serum electrolytes were increased and there was a moderate acidosis (Table 2). Clinistix reaction on urine was positive. Glucose was demonstrated in the feces.

Course in the hospital She improved on a soy flour formula with a low carbohydrate content (Mullsoy®). During the first half year she suffered frequent infections of the respiratory tract. The Clinistix reaction on the urine was sometimes weakly positive, sometimes negative. Different oral sugar loading tests were performed. The results of these, as well as of an intubation study leading to the diagnosis of glucose-galactose malabsorption, have been published elsewhere (28).

When, at about 6 months of age, she was given a fructose formula (30) the stools immediately became normal. Solid foods were introduced at 7 months and the daily volume of the fructose formula could successively be reduced. She weighed 7000 g when discharged from the hospital at 9 months of age.

History after discharge This was rather uneventful. To avoid loose stools she had, however to be maintained on a diet with certain limitations regarding milk and starch-containing foods. Oats seemed to be better tolerated than other cereals. From the age of 1 year she ate fructose formula only once or twice a day At 2 years she could tolerate 1 glass of milk, 2 sandwiches and 2 potatoes a day spaced over several meals, without any trouble. When 5 / years old her height was 107 cm and weight 17.9 kg. Physical and mental development was perfectly normal. She tolerated 2 glasses of milk a day 3–4 sandwiches and 3 potatoes. All fruits except grapes could be eaten without adverse consequences.

Case 5

A boy born on March 30, 1964 a younger brother of Case 4 was admitted at 4 days of age because of diarrhoea noted from the 4th day

History before admission. He was born 2 weeks after term and he had been breast fed. Due to severe diarrhoea, the stools resembling urine, he was transferred from the maternity hospital to the department of pediatrics.

On admission he weighed 500 g below his birth weight but his general condition was satisfactory Spontaneous motility was lively and he had a good appetite. He had a moderate decrease of turgor The presence of glucose in the stools and in the urine was demonstrated with the Clinistix test. Some other laboratory data are shown in Table 2.

Course in the hospital. Breast feeding was stopped and the infant instead received a fructose formula (30). The stools immediately became normal and the patient began to gain in weight.

The GTT and galactose TT resulted in flat blood glucose curves the fructose TT indicated a normal fructose absorption (Table 3 and 5).

History after discharge. For the next few months the patient was well. At 3 months of age he acquired a stomatitis, which was unsuccessfully treated with Chloromycetin, and he was therefore readmitted to the hospital.

On (second) admission he had a severe *Candida* infection is his mouth. His general condition worsened successively and the *Candida* infection spread to the skin. Soon he showed signs of respiratory insufficiency and the chest X-ray revealed pulmonary infiltrations.

ESR was 21 and the WBC varied between 22,500 and 8000 The differential count was normal (lymphocytes 53 and 66 per cent on two occasions). The total serum protein was low (4 1 g/100 ml). The paper electrophorogram, which had been normal at 2 weeks of age, was pathological with a borderline low albumin value (3 1 g/100 ml) and a low gammaglobulin value (0.1 g/100 ml). The α 2 globulin was relatively elevated (0.4 g/100 ml), whereas the α 1 and the β globulins were normal. The patient was found to have anti A and anti B isoagglutinins in his

---

After a modification with regard to salts this formula contains Calcium caseinate 2 3 %, corn oil 3.5 % fructose 4–8 %, and furthermore, per liter formula 1 Tsp. of a salt mixture (KCl, NaCl, $CaHPO_4$ $2H_2O$ mixture 2 1 1 w/w), 1 Tabl. Minovit® (a multivitamin and trace mineral preparation) and 1/2 1 Tsp. Nestargel® for adjustment of consistency

serum. On the immunoelectrophoresis there was weak γ-G band, γ-A and γ-M could not be distinguished. The patient died rather suddenly after two weeks in the hospital; he was thought to have aspirated during feeding.

Autopsy. No signs of widespread *Candida* infection of the gut or respiratory tract were found. The basal parts of the lungs were atelectatic; microscopically there were atelectatic parts in other lung segments too. An unspecific inflammatory picture with giant cells was seen in the bronchi with surrounding parenchyma, no epitheloid cells were found, and no mycelia were visible with special staining. The histological picture resembled *Pneumocystis Carinii* infection, but this organism was absent in the specimens. The thymus was macroscopically normal and weighed 5 g. Microscopically there was a rather marked atrophy of the lymphoid component of that organ. Lymph nodes from different parts of the body showed lymphoid atrophy with very small and indistinct secondary follicles and few reaction centres. The spleen showed atrophic Malpighian corpuscles without reaction centres. The histological preparations of the bone marrow were difficult to interpret with respect to the presence of small lymphocytes or plasma cells. The small intestine was strongly autolytic. There were no lymph follicles.

Case 6

A boy born on May 24, 1962, was admitted at 4 days of age because of diarrhoea from his 2nd day and fever from his 3rd day of life.

History before admission. A vacuum extractor was used at the otherwise normal delivery. He was breast fed for one week. Due to watery diarrhoea he lost 600 g of his weight in 4 days. A temperature of 38.4°C was recorded at the maternity department.

On admission, his general condition was fairly good, although a moderate decrease of skin turgor was observed. Spontaneous motility was lively and he had a good appetite.

The Clinitix test on the feces was strongly positive. Nearly 6 g of sugar, 2.7 g of which was glucose, was found per 100 g wet feces. The Clinitix test on the urine was sometimes positive and sometimes negative. Albuminuria was observed during the first 2 days after admission. At the same time the urinary sediment contained a considerable quantity of red and white blood cells and abundant crystals, but a new sediment a few days later was found to be normal. It was doubtful if the urinary tract was infected, sulfonamides were, however, given for a few days.

Course in the hospital. He continued to have profuse watery diarrhoea, and during the 4 days after admission he lost an additional 230 g in weight. By then he looked dehydrated and his motility decreased. The peripheral circulation seemed poor. Hyperelectrolytemia and metabolic acidosis were found (Table 2). The ECG was normal. During rehydration with intravenously administered fluid he had convulsions for 25 minutes. He increased his weight by 460 g within two days.

Replacement of mother's milk by a fructose formula (30) was followed by diminished diarrhoea and a fall of the fecal sugar content to less than 0.03 per cent of wet weight. The diet was abandoned, however because of vomiting and weight loss.

When the baby was 2 weeks old, tachycardia and ventricular extrasystoles were observed and general adynamia occurred. Serum potassium was normal and there were no signs of hypokalemia on the ECG. Nevertheless, potassium chloride was given orally. The next day pulmonary congestion and a considerable enlargement of the heart was seen on X-ray. During the next few days the tachycardia increased and the liver became enlarged. Shifting ECG findings occurred with increased PR-interval, transient extrasystoles and negative T-waves over the left ventricle. The pulse rate and heart size gradually became normal during the following weeks. The clinical course of this complication was consistent with the diagnosis of infantile myocarditis. Virus isolation from the feces was negative and the serum did not contain neutralizing antibodies against Cox-Sackie B virus. Feces cultures showed a pathogenic strain of E. coli, and the patient was given broad spectrum antibiotics. In a few days he developed a widespread staphylococcal dermatitis in the face and the axillary regions. The feces now contained a dominating flora of *Staphylococcus aureus*.

The diet had been changed to a soy flour formula with a low carbohydrate content (Mullsoy®) with extra amounts of water. Weight gain was slow and he had 2–3 semisolid stools a day. From 1 month of age limited amounts of the fructose formula were added without ill effects.

At the age of about two months a definite diagnosis of GGM was secured by oral sugar loading tests including a GTT and a galactose TT which resulted in flat blood sugar curves and increased fecal sugar. From that age the patient was consequently fed the fructose formula (30) after which the diarrhoea subsided. He was nearly 10 weeks old when he finally attained his birth weight again. Subsequently his growth was rapid and he gradually reached a normal weight in relation to his length. He was discharged at 6 months of age when his body weight was 6500 g.

History after discharge. The daily amounts of the fructose formula could be reduced as the amount of solid food was successively increased. At the age of 1 year he received about 200 g of the fructose formula twice a day. Otherwise he ate egg, fish, meat, vegetables and fruit. He tolerated a up to 300 ml of cream a day. He refused oat meal porridge which earlier he had tolerated in limited amounts. He also disliked potatoes. One slice of white bread resulted in diarrhoea.

Successive studies showed that the physical and mental development of this boy has been normal. At 5 1/2 years of age he was 112 cm tall and weighed 17 kg. His belly has a tendency to swell when he eats

unsuitable food. He then experiences abdominal pains but loose stools do not always follow The symptoms are provoked by foodstuffs rich in ordinary sugar or still more by starch. Milk is tolerated fairly well. He still dislikes potatoes, but eats large quantities of vegetables and fish every day From 3 / years of age no fructose has been added to his diet.

Relevant symptoms and signs of Glucose Galactose malabsorption as evaluated from the case histories

The patients have had several features in common (Table 1–3) The diarrhoea started within a few days after birth. The time of onset varied a little, probably depending on how much the babies suckled They gradually became dehydrated and often a moderate fever was noted The general condition was always remarkably good in the beginning, and the cases observed by us from an early age had a striking appetite, probably depending on thirst, as long as they were not extremely dehydrated. The stools were watery and resembled urine, giving rise in some cases, to a strong suspicion of a congenital communication between the rectum and the urinary tract.

The stools always contained several per cent of carbohydrate. The Clinistix test (specific for glucose) on the watery stools was strongly positive. The blood glucose level was usually low during the first months of life (Table 3) and after breast milk or ordinary formula feeding it did not rise above the fasting level.

The Clinistix test on urine was sometimes positive and sometimes negative independent of the clinical state

Before the diagnosis was recognized, the patients usually have been dietetically treated as having severe gastroenteritis. During periods of intravenous nutrition oral amounts of glucose seemed to be tolerated as long as the concentration was below 2–3 per cent. Similarly small amounts of breast milk were fairly well tolerated, unless given as the main nutritional source, when the patient soon deteriorated The prompt cessation of the watery diarrhoea when fructose was given as a substitute for all other dietary carbohydrates was always quite remarkable.

Mental and physical development after cessation of continuous diarrhoea has been normal in all surviving patients.

Besides the sugar diarrhoea and the slight glucosuria, additional illnesses occurred in 5 patients (Table 1) Renal concrements occurred in Cases 1 and 3 In Case 2 nephrocalcinosis was found at autopsy Fungus infection with *Candida albicans* was found in two cases. Both of these died. This rather common stomatitis in early infancy did not seem to have contributed to the death of Case 2. In Case 5 the fungus infection spread to the skin, but at autopsy there were no signs of invasion of internal organs.

BIOCHEMISTRY OF INTESTINAL FUNCTION

Methods

Reagents

Analytical grade reagents were used for the chemical analyses. Sugars were obtained from May & Baker Ltd., Dagenham, England, from Pfanstiehl Laboratories Inc., Waukegan, Ill. USA and from Mallinkrodt Chem. Works, New York, N Y USA. Buffers were prepared as proposed by Gomori (13) using reagents from Merck A. G Darmstadt, Germany TRIS, however was purchased from Sigma Chem. Co St Louis, Mo USA. Peroxidase (horse-radish) also came from Sigma. Glucose oxidase (crude) was obtained from Worthington Biochem. Corp., Freehold, N J USA. Galactose oxidase was from the same source initially but was later replaced by the preparation of Miles Chem. Co., Elkhart, Ind, USA. O-dianisidine (3 3-dimethoxyl benzidine) was obtained from Eastman Org. Chemicals as was *p*-bromo aniline for the xylose determination. The detergent Cascade was from May & Baker β-indole acetic acid for fructose determination was obtained from Merck and so was anthrone. Polyethylene glycol (MW 4000) was manufactured by Bergmans fabriker Gnesta, Sweden. The lactase, invertase and maltase preparations were generous gifts from Mycopharm, Delft, Netherlands.

General procedures

Oral sugar tolerance tests 10 % sugar solutions were given in a dose of 2 g sugar/kg body

weight. The adult patient received doses of 50 g. The accuracy in feces collection during the 48 hours after some of these tests could be estimated by adding 1–5 g of an unabsorbed marker polyethylene glycol (PEG), to the test dose. For the xylose absorption test doses of 15 g D-xylose/sq.m. body surface area were used.

Intubation studies for the measurement of intestinal absorption of sugars were performed with rubber or polyvinyl tubes of an inner diameter of 2 mm, which were passed under fluoroscopic control through the nose into the jejunum. Homogenized test meals of 200–300 ml containing 3% casein, 4% corn oil, salts as present in the fructose formula (*vide supra*), 1 % PEG and 4 % of various sugar mixtures were given orally. The intestinal contents were siphoned into ice-chilled test tubes and fractions were collected for 2 hours. The test tubes were frozen at −20 C and kept in a deep freezer until analysis was performed.

The percentage digestion and absorption was calculated as per cent of the initial amount of sugar. It was assumed that all the sugar which had been absorbed had also been hydrolysed to monosaccharides. The percentage of disaccharide *digested* was calculated from the initial amount minus the amount recovered as disaccharide. The percentage of sugar *absorbed* was calculated from the initial amount minus the amount of this sugar recovered (disaccharide plus monosaccharide). The following equation was used to compensate for volume changes:

$100\ [1-(P \times S)/(P \times S)] = \%$ digestion or absorption, respectively

P and P are the concentrations of PEG in the test meal and sample, respectively and S, and S the corresponding concentrations of sugar. PEG concentration was determined according to Hydén (20).

Deproteinization of biological samples. Blood, intestinal content, test meals and suspensions of feces were precipitated with 2 *ml* 0.3 *N* $Ba(OH)_2$ and 2 ml equimolar $ZnSO$ per 1 ml sample after addition of a suitable amount of water and were centrifuged or filtered (50). Previous to this method the feces suspensions had been diluted at least ten-fold with water to obtain clear colourless filtrates after deproteinization.

Sugar determinations

Unspecific methods. 1. Reducing sugar was determined using the Somogyi-Nelson method (51) with relevant sugars as standards. All sugars except sucrose are reducing.

2. Total sugar was measured using an anthrone method (46). All sugars as well as polysaccharides react.

3. Qualitative identification of sugars was done by paper chromatography. Descending chromatograms of some feces samples were thus made on Whatman 1 paper. The solvent used was a mixture of ethyl acetate, glacial acetic acid and water (9 : 2 : 2, v/v). The dried chromatograms were developed with aniline phthalate (45).

Specific methods. 1. Glucose was assayed using a glucose oxidase reagent (10). In the presence of TRIS only free glucose is measured.

2. Galactose was measured similarly to glucose using galactose oxidase. Free galactose, and also lactose to a small extent, act as substrates. If present, corrections were made for lactose content. It must be mentioned that the photometer readings are not quite proportional to the sugar concentration. Hence, standard curves with several concentrations of sugar were made for each set of determinations. The reagent was prepared as follows. 10 mg dry galactose oxidase (Miles), 0.5 mg peroxidase, 0.5 ml o-dianisidine as a saturated solution in alcohol and a detergent, 1 ml Cascade (10 % in alcohol), were added to 100 ml potassium phosphate buffer (0.1 *M*, pH 7).

3. Fructose was assayed using Heyrovsky's method (18) measuring keto-sugars and their derivatives (sucrose, inulin). Glucose reacts slightly to about 1.3 % of the colour produced by fructose. When appreciable amounts of glucose were present, the appropriate corrections

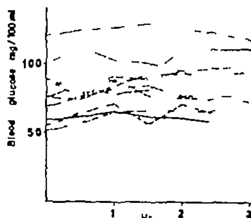


Fig 1 Oral glucose tolerance tests in 5 patients with glucose galactose malabsorption.
Symbols: ——— Case 1 Case 3 ----- Case 4 - - - Case 5, - - Case 6. *Note:* The maximum increase of blood glucose observed within the first hour in any patient is 21 mg/100 ml.

were made. In one experiment fructose had to be determined in the presence of sucrose, which was determined separately (*vide infra*) and subtracted from the total fructose value to obtain the concentration of free fructose

4 Xylose was determined according to O Brien and Ibbott (42)

5 Disaccharides (lactose sucrose and maltose) were assayed enzymatically by measuring the increase in glucose content in a deproteinized and suitably diluted sample on incubation with a disaccharidase preparation.

a. Lactose. A lactase solution was prepared by dissolving 50 mg of dry lactase in 100 ml potassium phosphate buffer (0 1 *M* pH 6.8). This solution was filtered after 20 minutes intermittent stirring at room temperature. In a test tube 1 ml deproteinized sample (containing less than 100 μg free glucose and lactose-bound glucose) was incubated at 37 C for 20 minutes with 1 ml lactase solution. The increase in glucose content was measured using TRIS glucose oxidase (10). This increase multiplied by a factor of 2 corresponds to the lactose monohydrate content of the sample. Standard solutions of lactose and glucose were treated similarly In each series of determinations samples with added lactose were included to check that complete hydrolysis by lactase occurred.

b Sucrose. The disaccharidase solution was made by dissolving 10 mg of dry invertase in 100 ml sodium acetate buffer (0 1 *M* pH 4.5). As with the lactose determination, samples were incubated with the disaccharidase solution, and the sucrose content was calculated from the increase in the glucose content.

c Maltose. A one-step method was used to determine the maltose monohydrate *plus* glucose content of the intestinal contents. The reagent was prepared by dissolving 200 mg dry maltase in 50 ml potassium phosphate buffer (0 1 *M* pH 5 8). The filtered solution was added to 50 ml glucose oxidase reagent prepared using the same buffer This latter reagent contained 200 mg crude glucose oxidase, 0.5 mg peroxidase, 0.5 ml saturated o-dianisidine in alcohol and 1 ml 10 % Cascade (in alcohol). In a test tube 1 ml deproteinized sample (containing less than 50 μg glucose and maltose together) and 2 ml of the maltase glucose oxidase reagent were incubated at 37°C for 60 minutes. Extinctions were read with the same photometer as used for glucose determination at wave length 420 mμ Standard solutions of maltose and samples with added maltose were treated similarly for each set of determinations. The maltose content was calculated from the glucose estimated, by subtraction of the initially present glucose as assayed using the TRIS glucose oxidase reagent.

Determination of daily fat excretion

Stools were collected for 4–6 days and stored frozen. After homogenization duplicate determinations were carried out by the method of van de Kamer (22)

Results

Response of blood sugar to oral sugar tolerance tests (TT) The results of all *GTT's* are plotted in Fig. 1 Most of the cases were tested more than once. The curves are flat, but increases in blood sugar up to 21 mg/100 ml within 60 minutes may occur (Table 3)

Galactose TT's were performed in Cases 1 5 and 6 As seen in Table 4 the rise of galactose was insignificant in comparison with the controls. The rise of glucose was also very small or absent but this was true of the controls too *Lactose* TT's were performed in Cases 1 4 and 6 the maximal rise of blood glucose was 16 mg/100 ml (Table 3) In Case 4 a *sucrose* TT was made also (28) the blood glucose rose 42 mg/100 ml during the first hour

The *fructose* TT performed on the patients soon after admission and before amelioration of the symptoms used to result in significant increase in the blood glucose (Fig. 2) In Case 6 a flatter curve was obtained later on (the

Table 3. *Résumé of routine sugar analyses in six cases with glucose-galactose malabsorption*

Case nr	Blood glucose fasting value (mg/100 ml)	Glucose TT max. increase within 60 min (mg/100 ml)	Lactose TT max. increase within 60 min (mg/100 ml)	Sugar in feces (Clinistix)	Sugar in urine
1	70–110[a]	4	8	+ + +	±
2	Not done	Not done	Not done	Not done	+
3[b]	78–110	21	Not done	Not done	±
4	39–75	16	16	+ +	±
5	51–80	14	Not done	+ +	±
6	57–76	13	1	+ + +	±

Hagedorn & Jensen method (16). At 3½ years fasting blood sugar was 59–65 with a glucose oxidase method. The other glucose values in this table are obtained with glucose oxidase reagent.
[a] Only examined with reduction method (2, 41). Other patients measured with Clinitest.
Adult patient.

curve with the lowest value at one hour) this patient had for some time been fed a formula with a relatively high fructose content. The significance of different responses in blood glucose after oral fructose loads will be discussed in another paper (38).

X)*lose absorption tests have been per*formed in Cases 5 and 6 (Table 5). The results showed subnormal and borderline values, respectively for xylose in blood (36). The xylose excretion in urine was subnormal too (43).

Fecal sugar measurements after oral sugar loads. Table 6 summarizes the results of fecal sugar measurements following sugar loading tests in Cases 1, 4, 5 and 6. The results of some measurements in Case 6 are also given graphically (Fig. 3). As a check on the chemical determinations some of the stool portions from Case 6, as indicated by numbers on the columns, were chromatographed (Fig. 4 B). Fig. 4 A is a chromatogram of stool filtrate from the same patient while he was fed breast milk, when the chromatogram was performed the total fecal sugar content amounted to 5.8 *g/100 ml wet feces.*

Glucose, galactose and lactose (but not fructose) loads of 2 g/kg body weight, given during the first 6 months of life, consistently resulted in increased diarrhoea with a marked rise in the fecal sugar excretion (Cases 4–6). It should also be noted that the excretion of galactose was always much higher than that of glucose.

In Case *1 (3 ½ years of age) the GTT was* not followed by increased sugar in the stools. The day previous to the performance of the

Table 4. *Oral galactose tolerance tests in 3 patients with glucose-galactose malabsorption and 4 controls*
Galactose values within brackets were measured with the galactose oxidase reagent, the other values with Somogyi-Nelson method with subtraction of blood glucose.

Subject	Sex	Age	Glucose rise, mg/100 ml		Galactose rise, mg/100 ml	
			30 min	60 min	30 min	60 min
Case 1	♀	3 yrs	1	−7	0	0
Case 5	♂	4 mo	5	4	10	3
Case 6	♂	2 mos	5	−2		
Case 6	♂	5 mos	−3	6	(<10)	(<10)
Control 1		7 mos	2	2	49 (51)	105 (83)
Control 2	♀	1 yr	9	8	45 (63)	110 (140)
Control 3	♂	6 yrs	24	16	66 (56)	78 (73)
Control 4	♀	9 yrs	10	0	15 (29)	83 (91)

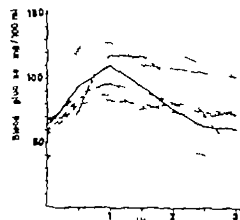


Fig 2 Oral fructose tolerance tests in 5 patients with glucose-galactose malabsorption.
Symbols: ——— Case 1 Case 3 - - - - - Case 4 - - - Case 5 - - *Note* The increase of blood glucose within the first hour varies considerably (between 7 and 81 mg/100 ml) but usually it exceeds 20 mg/100 ml.

GTT a higher glucose value in the feces was observed, 1 14 % of feces wet weight as compared with 0 07 % at the test, a fact probably due to the diet including a lunch with as a dessert frozen raspberries and sugar In Case 3 (examined in adulthood) it was considered useless to look for fecal sugars after the oral tolerance tests, since diarrhoea did not result.

Intubation studies These studies were performed in Cases 1 3 and 4 after intubation of the upper jejunum. Comparison of the glucose and fructose absorption after administration of a test meal containing both of these sugars in equal concentrations was found to be of great value for the diagnosis of GGM. glucose was always absorbed more slowly than fructose (28 29) In Cases 1 and 4 intubation studies were also performed with test meals containing

Table 5 *Xylose absorption tests in two infants with glucose-galactose malabsorption*

Test dose 15 g/sq.m. body surface

Case nr	Age (months)	Blood xylose mg/100 ml		Urinary xylose % of dose excreted in 8 hours
		30 min	60 min	
5	/	9	15	5
6	13	15	25	9

Table 6. *Per cent excretion of sugar in feces within 48 hours after oral administration of different sugars (2 g/kg body wt) together with PEG*

Subject	Age	Sugar tested	Recovery (% of test dose)	
			Sugar	PEG
Case 5	/₄ mo	Glucose	39	—
		Galactose	83	76
		Fructose	1 4	58
Case 6	2 mos	Glucose	22	74
		Fructose	0 7	94
		Galactose	53	83
Case 6	5 mos	Glucose	39	84
		Galactose	60	96
		Fructose	0.3	70
		Lactose	10[a]	48
Case 4	4 mos	Lactose	13.5[b]	—
	6 mos	Fructose	1.9	—
Case 1	3 / ys	Glucose	0 7	66
		Lactose	<8.5	96
		Fructose	0.4	116

Sum of lactose, glucose and galactose measured with specific enzymatic methods. (1.5 % of the test dose was recovered as the unsplit disaccharide; the rest of the fecal sugar was /₃ glucose and / galactose.)

[b] Sum of lactose, glucose and galactose. Lactose and galactose were measured as excess of sugar found by a reduction method after determination of glucose and fructose with specific methods.

As *b*, but anthrone method for total sugar

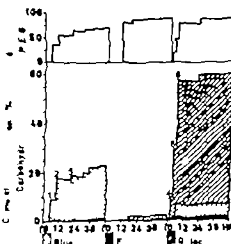


Fig 3 Cumulative excretion in feces of PEG and sugars during 48 hours after oral sugar tolerance tests with glucose, fructose and galactose, respectively in a dose of 2 g per kg body weight, Case 6, aged 2 months. The number on the columns refer to stool portions which were also chromatographed (See Fig. 4 *B*). *Note* The fecal excretion of galactose was about 2 / times that of glucose After the fructose loading only insignificant amounts of sugar (glucose) could be demonstrated.

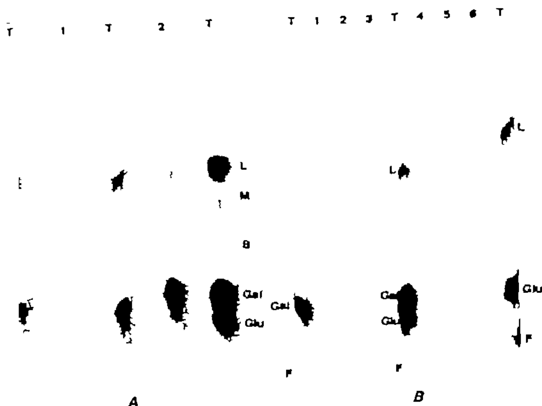


Fig. 4 *A*, *B*. Descending paper chromatograms of extracts of feces (starting points at the top of the figure). Symbols: T sugar test solutions; L, lactose; M, maltose; S, sucrose; *Gal*, *galactose*, *Glu*, *glucose* F fructose. Solvent of ethyl acetate, acetic acid and water (9 2 2, v/v). Development with aniline phthalate.

A Case 6, aged 9 days, diet, breast milk. Samples 1 and 2 are derived from the same stool; sample 2 contained twice as much extract as sample 1 *Note:* Fecal sugar consists mainly of galactose and glucose. Above moderate lactose spot there are at least 2 unidentified compounds.

B. Case 6, aged 2 months; diet, soy flour formula. Samples 1, 2 and 3 are derived from stools following GTT and samples 4 5 and 6 from stools following galactose TT *Note:* The glucose spot of sample 6 is obviously from sucrose and glucose in the diet given before and after the test (see also Fig. 3).

other carbohydrate mixtures than glucose and fructose. A typical experiment is portrayed graphically in Fig. 5 The data from this and from similar studies in Cases 1 and 4 are presented in Table 7 The degree of hydrolysis in the upper jejunum was about 25 % for lactose and about 30 % for sucrose and maltose. The luminal concentrations of glucose were higher than those of fructose when sucrose was given in the test meal, indicating that the absorption of glucose was slower than that of fructose (Table 7 Case 4 last experiment).

On several occasions it was found that the fasting patient with GGM had measurable amounts of glucose in the first specimens of *intestinal juice before the test meal had* reached the level of intubation. In Case 1 when a test meal without carbohydrate was given, the contents of the jejunum also contained significant amounts of glucose (13 mg/100 ml). When a new test meal containing 3.5 *per cent fructose was given, slightly higher* values of glucose (maximum 35 mg/100 ml) resulted. During this study the blood glucose varied between 72 and 85 mg/100 ml. In Case 4 before the administration of the xylose-fructose mixture, the fasting glucose concentration of the intestinal juice was 19 mg/100 ml. There

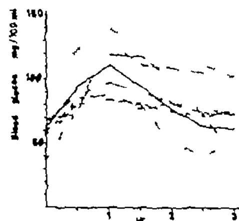


Fig 2 Oral fructose tolerance tests in 5 patients with glucose-galactose malabsorption.
Symbols ——— Case 1 Case 3 - - - - -
Case 4 — - — Case 5 — - *Note* The increase of blood glucose within the first hour varies considerably (between 7 and 81 mg/100 ml) but usually it exceeds 20 mg/100 ml.

GTT a higher glucose value in the feces was observed, 1 14 % of feces wet weight as compared with 0 07 % at the test, a fact probably due to the diet including a lunch with as a dessert frozen raspberries and sugar In Case 3 (examined in adulthood) it was considered useless to look for fecal sugars after the oral tolerance tests, since diarrhoea did not result.

Intubation studies These studies were performed in Cases 1 3 and 4 after intubation of the upper jejunum Comparison of the glucose and fructose absorption after administration of a test meal containing both of these sugars in equal concentrations was found to be of great value for the diagnosis of GGM glucose was always absorbed more slowly than fructose (28 29) In Cases 1 and 4 intubation studies were also performed with test meals containing

Table 5 *Xylose absorption tests in two infants with glucose-galactose malabsorption*

Test dose 15 g/sq.m. body surface

Case nr	Age (months)	Blood xylose mg/100 ml		Urinary xylose % of dose excreted in 8 hours
		30 min	60 min	
5	1	9	15	5
6	13	15	25	9

Table 6. *Per cent excretion of sugar in feces within 48 hours after oral administration of different sugars (2 g/kg body wt) together with PEG*

Subject	Age	Sugar tested	Recovery (% of test dose)	
			Sugar	PEG
Case 5	1 mo	Glucose	39	—
		Galactose	83	76
		Fructose	1 4	58
Case 6	2 mos	Glucose	22	74
		Fructose	0,7	94
		Galactose	53	83
Case 6	5 mos	Glucose	39	84
		Galactose	60	96
		Fructose	0,3	70
		Lactose	10[a]	48
Case 4	4 mos	Lactose	13,5[b]	—
	6 mos	Fructose	1,9	—
Case 1	3 /4 yrs	Glucose	0,7	66
		Lactose	<8,5	96
		Fructose	0,4	116

[a] Sum of lactose, glucose and galactose measured with specific enzymatic methods. (1.5 % of the test dose was recovered as the unsplit disaccharide, the rest of the fecal sugar was 1/4 glucose and 3/4 galactose.)
[b] Sum of lactose, glucose and galactose. Lactose and galactose were measured as excess of sugar found by a reduction method after determination of glucose and fructose with specific methods.
[c] As *b*, but anthrone method for total sugar

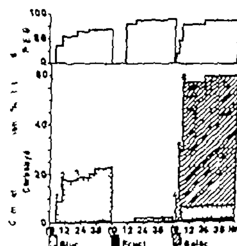


Fig 3 Cumulative excretion in feces of PEG and sugars during 48 hours after oral sugar tolerance tests with glucose, fructose and galactose respectively in a dose of 2 g per kg body weight, Case 6, aged 2 months. The number on the columns refer to stool portions which were also chromatographed (See Fig. 4 B). *Note* The fecal excretion of galactose was about 2 / times that of glucose. After the fructose loading only insignificant amounts of sugar (glucose) could be demonstrated.

scribed by Anderson *et al.* (3) died at 3 months, whilst under medical treatment, in a state of inanition and dehydration. Several relatives to the 6 cases presented here died at 1 3 months of age, probably due to GGM (cf. p. 21).

Diagnosis of glucose-galactose malabsorption. The summary of symptoms presented according to these case histories cannot be regarded as entirely pathognomonic for GGM. Almost the same symptoms are seen in congenital lactase deficiency but the combination of glucose in the watery feces and of a slight glucosuria despite low blood sugar levels is highly suggestive towards the diagnosis of GGM. The condition can also be confused with the recently described transient malabsorption of monosaccharides (8), which seems to have an infectious etiology. The results of the sugar loading tests and of the dietetic trial with a formula, in which fructose is the only carbohydrate, show that during the first months of life a guaranteed diagnosis can be made without further investigations. However sugar determinations on the stools passed after the oral sugar loads should not be neglected. In Case 1 (3 1/2 years of age) and Case 3 (adult) no sugar diarrhoea was observed after the sugar TT's. Hence, in patients out of infancy it may be necessary to perform an intubation study with measurement of the relative absorption coefficients of glucose and fructose, in order to obtain a reliable diagnosis.

Some laboratory tests carried out in order to exclude other diarrhoic conditions may give confusing results. A moderate steatorrhea is sometimes found, as observed in Case 1 and in patients reported by others (3 25). This probably results from a short intestinal passage time. Steatorrhea has also been observed in patients with lactase deficiency (24). Laplane *et al.* (25) reported that, when giving 25 g of glucose in addition to a barium meal, a "bataille péristaltique" occurred after a short latent period and at fluoroscopy the barium was then seen to have reached the rectum immediately. The same phenomenon has been observed in patients with lactase (or sucrase) deficiency after the addition of lactose (or sucrose) to a barium meal (27).

Although the histological appearance of the mucosa is normal in GGM (3 37 48) low or borderline values for xylose absorption have been observed in Cases 5 and 6 as well as in other cases of GGM in the literature (1 3 25). This finding could be taken as a sign of general malabsorption. Realizing that under normal conditions xylose is partly absorbed by the active sugar transport mechanism (7 47) the low xylose absorption in patients with GGM may however be explained without the assumption of an unspecific damage to the intestinal mucosa. The active transport mechanism accounting for the major part of the transport of certain sugars, carries only a minor part of the xylose transport, it has been claimed that the major part passes between the epithelial cells (52).

Cause of hyperosmolarity. As judged from the serum electrolyte values (Table 2) the patients suffered from hyperosmolar dehydration when the diarrhoea was at its worst. In adult patients with lactase deficiency it has been shown that, during perfusion of a 1 meter long section of jejunum with a slightly hypotonic solution containing 9 % lactose, a net flux of water occurs into the intestinal lumen (23). This is in contrast with the finding in normal subjects when lactose perfusion causes net absorption of water. In a recent study (26) in infants with congenital lactase deficiency it was found that infusion into the stomach of a solution containing 5.4 % lactose resulted in a net secretion of water over the whole length of the small intestine. The simultaneous loss of sodium from the blood into the small intestine was comparatively small, and moreover, the colon seemed to reabsorb sodium more effectively than water. Similarly when, in patients with GGM, the lactose of breast milk (lactose content 7 %) is gradually hydrolyzed by the mucosal lactase, and the absorption of the resulting monosaccharides, glucose and galactose, is very slow, the intesti-

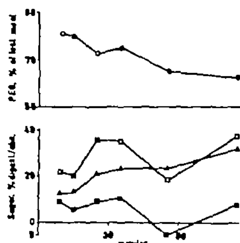


Fig 5 Percentage digestion and absorption of sugars in the upper jejunum (2nd loop) after administration of a test meal containing 2 per cent fructose, 2 per cent maltose and 1 per cent PEG Case 4 aged 7 months. *Symbols.* ○ PEG □ maltose (% digested) ▲, fructose (% absorbed) ■, glucose (% absorbed). *Note* Maltose was hydrolyzed to 20–40 per cent. Less than half of the released glucose was absorbed at this level of the intestine (see also Table 7).

was a small increase in the glucose concentration during the rest of the study with a maximum value of 40 mg/100 ml, but as in Case 1 this increase could at least partly be ascribed to traces of glucose present in the fructose.

Fecal fat determinations Fecal fat has been measured in Cases 1 and 4 When these patients received a soy flour formula steatorrhea was absent. When fed breast milk Case 1 was found to have an average excretion of 15.4 g fecal fat per day

DISCUSSION

Delineation of the disorder

Natural history of glucose-galactose malabsorption. The typical course of untreated GGM is illustrated by Case 2, who died at an age of about 7 weeks, shortly after admission to the hospital. Her clinical picture resembled that of the other cases, and being a sister of Case 1 there is little doubt regarding the diagnosis. Probably she would have died earlier if breast feeding had been continued for longer than two weeks after birth. A sibling of a case described by Laplane *et al* (25) died as early as at the age of 8 days. A brother of the patient de

Table 7 *Percentage digestion and absorption of sugars in upper jejunum after administration of test meals as observed in intubation studies*

The values given are averages from 5–8 samples collected for 90 minutes.
Case 1 aged 3½ years and Case 4 7 months.

Case nr	Intubation site	PEG (% of test meal)	Sugars in test meal	% digestion	% absorption
1	1st jej. loop	56	Fructose 2	—	32
			Glucose 2 %	—	6
1	1st jej. loop	38	Fructose 2	—	43
			Lactose 2 %	22	(glu)-3[a]
4[b]	2nd jej. loop	50	Fructose 2 %	—	31
			Glucose 2	—	18
4	2nd jej. loop	74	Fructose 2 %	—	20
			Maltose 2	31	7
4	2nd jej loop	59	Fructose 2 %	—	22
			Glucose 1 %	—	9
			Galactose 1 %	—	—
4	2nd jej loop	67	Fructose 2 %	—	33
			Lactose 2 %	26	(glu) 3[a]
4	2nd jej loop	54	Xylose 2 %	—	17
			Fructose 2 %	—	33
4	2nd jej. loop	54	Xylose 2 %2	—	12
			Sucrose 2 %	29	(fru) 11
					(glu) 7

[a] Galactose absorption was not evaluated.
[b] The first intubation study of Case 4 was done 4 weeks before the other studies, which were performed during the course of 4 days with the tube remaining in position.

only small amounts of starch, milk and sugar Therefore, some discomforts such as abdominal cramps, flatulence and occasional loose stools have to be accepted.

Pathophysiological considerations

As could be anticipated from the dietetic trials where limited amounts of approximately half isotonic glucose solutions did not increase the diarrhoea, the biochemical investigations revealed that there is *some* absorption of glucose. The GTT's of Fig. 1 invariably show a small increase in the blood sugar at 1 hour The intubation studies (Table 7) give further evidence towards this conclusion. The larger amount of galactose recovered from the feces compared with that of glucose after loading with the respective sugars indicates that galactose is absorbed even more slowly than glucose. The level of blood galactose at the galactose TT's (Table 4) does not significantly differ from zero. As most of the sugar recovered from the feces appeared within the first 6 hours after the oral loading, it is not likely that a different metabolism by the bacterial flora accounts for the difference in the excretion of glucose and galactose. It has been shown in congenital sucrase deficiency that, when after an oral test dose of sucrose the concentration of sugar in the stools is at maximum (i.e. within 6 hours) there is still comparably little lactic acid, the main bacterial metabolite of unabsorbed sugar (44). Our results are at variance with those of Anderson *et al.* (3) who found less galactose (37 % of the dose) than glucose (59 % of the dose) in the stools after similar tolerance tests in one patient with GGM. However they collected the stools for only a 6 hour period and did not test the reliability of collection by e.g. using an unabsorbable marker Using ^{14}C-labelled glucose and galactose, Linneweh *et al* (33) found in a case of GGM a higher radioactivity in serum after the administration of glucose than after administration of galactose. The absorption of glucose was calculated to be nearly twice that of galactose, but this difference was not commented upon.

Under normal conditions galactose is, in man as well as in many other species, absorbed somewhat faster than glucose when these sugars are given separately (4 19) In the patients with GGM the observed concentration of glucose in the fasting intestinal content, and when sugars other than glucose were administered, was not high enough to assume influence of a competitive inhibition of galactose absorption. The residual absorption of glucose, found to be better than that of galactose, cannot be explained by simple diffusion or reduced rate of transport by the mechanism normally responsible for the bulk of the transport of these hexoses. In patients with GGM, at least part of the glucose seems to be absorbed by a second specific pathway for glucose having a much lower affinity for galactose. This proposed second pathway for glucose absorption has already been speculated upon because of irregularities in the mutual inhibition of the intestinal transport of glucose and galactose (39) If it exists, this second pathway resembles the tubular reabsorption process for glucose, which also has a higher affinity for glucose than for galactose (49)

The concentration of glucose found in the fasting intestinal lumen (13 and 19 mg/100 ml, respectively in the two patients in which this was measured) was below the blood sugar concentration. This does not imply that active absorption still occurs. If merely small amounts of glucose are exchanged between the epithelial cells and the luminal content, the rather low intestinal glucose concentration could be due to dilution by secretions, provided that these are practically glucose-free.

In the adult jejunum, the hydrolysis of sucrose is, under normal conditions, not rate-limiting for the absorption of this sugar (14) There is no reason to believe that the interrelationship between sucrose hydrolysis and subsequent monosaccharide absorption is different in children. During sucrose absorption the intraluminal concentration of monosac-

nal wall will secrete water into the lumen to maintain isotonicity Disregarding the electrolytes and other solutes in the intestinal juice, the mixture of glucose and galactose must be diluted to 5 5 per cent to be isotonic. By this mechanism the body will lose large amounts of water without a proportional loss of electrolytes. The same situation arises when the patients consume starch, which is gradually converted to glucose. It is thus quite natural that the babies receiving large amounts of carbohydrates such as lactose and starch become very thirsty As extra water was not given, hyperosmolarity resulted. The renal tubular concentration mechanism, presumably working at maximal capacity is apparently insufficient to compensate for the hyperosmolarity

Additional disorders The necessity to produce maximally concentrated urine during long periods is a possible explanation for the nephrocalcinosis found at autopsy in Case 2 and for the development of stones in the urinary tract of Case 1 at an unusually early age. In Case 3 the same mechanism may have been responsible.

Case 5 was born at a time when GGM was a well defined entity and it was therefore diagnosed at an early age and successfully treated. His death at 4 months seems to be related to an agammaglobulinaemia. Unfortunately no diagnosis of the type could be made since he died soon after the second admission. The agammaglobulinaemia, however was probably coincidental and unrelated to the disturbed absorption of glucose and galactose

In the history of Case 6 there were also several complications, including an infantile myocarditis which could not be ascribed to the congenitally disturbed carbohydrate absorption or to secondary malnutrition of important nutritive factors. The initial dietary trials were, it is true, not quite adequate but vitamins, salts and trace minerals were added in sufficient amounts.

Treatment and prognosis Case 3 the adult woman, is probably unique, as she survived before the era of parenteral fluid therapy For her it was advantageous that her mother's lactation ceased early and that she was then given a very unorthodox feeding with a low carbohydrate content. Case 1 4 and 6 were also given diets with a low carbohydrate content (Mullsoy) before the diagnosis was established. The amelioration of the diarrhoea observed when feeding this diet is not only due to a low carbohydrate content but also to the fact that the main carbohydrate component is sucrose. After splitting by intestinal invertase the fructose part of sucrose is well absorbed. However the best therapeutic response in babies was achieved by feeding a formula containing fructose (4–8 per cent) as the only carbohydrate ingredient, this being the logical consequence of the experimental findings. In one patient (Case 6) the therapeutic trial with fructose was misleading; although the diarrhoea improved the patient started to vomit. This cannot be readily explained, but the rather high casein content of the formula may have played a role. Later the formula was well tolerated.

The reduction of clinical symptoms after oral sugar tolerance tests parallels the increased tolerance to dietary carbohydrates with increasing age. The experimental data of the present and previous studies (29 37) gave no evidence of a more rapid absorption with increasing age. The adaptation is therefore illusory and is probably the result of a combination of factors. (1) the size of the intestinal tract increases more than the caloric needs and the intake of carbohydrates (2) due to a longer intestinal passage time beyond infancy a larger part of a test dose can be absorbed, and (3) the bacterial flora has more time to metabolize the sugar Furthermore, because of the consumption of a diet containing badly absorbed carbohydrates, the older patients may have developed a larger saccharolytic bacterial flora.

If recognized in time, GGM has a favourable prognosis with correct dietetic measures the development of the children both physically as well as mentally is normal. As the patient grows up it becomes increasingly impractical to adhere to a strict diet containing

Acta Pædiat Scand Suppl 188 1969

GLUCOSE-GALACTOSE MALABSORPTION

A Genetic Study

K. MELIN and G W MEEUWISSE

Department of Pediatrics, University of Umeå, S rden, and Department of Pediatrics, University of Lund, Sweden

Glucose-galactose malabsorption (GGM) is, as described in the previous pages, a congenital disorder characterized by watery acid mel-litorrhea from birth. Practically all the re ported cases of GGM have a mild glucosuria. that of Dubois *et al.* (12) is an exception.

In a preliminary report we mentioned 3 re lated, female cases of GGM where the parents were all mutually related (31). GGM was concluded to be a recessively inherited disorder In a later communication a male case was reported (32). The present article contains a detailed pedigree. In order to find a method of detecting heterozygotes, biochemical investigations on carbohydrate metabolism were undertaken on parents of some of the patients with GGM. The pattern of amino acid excretion by the kidney was studied in five of the patients and their parents.

MATERIAL AND METHODS

The patients, coded 1-6 (Fig. 1), were presented with their case histories in the previous pages. Cases 2 and 5 died in the hospital at the age of 3 and 4 months, respectively Cases 1 4 and 6 are children, aged 10, 7 and 6 years, respectively Case 3 is now woman of 42.

Abbreviations: β-AIB, β-amino isobutyric acid, GGM, glucose-galactose malabsorption; GTT glucose tolerance test.

The pedigree has been made up from data gathered through numerous interviews among relatives of the patients and from parish registers, of which photocopies are available at the city library of Umeå. The ancestors on the top f Fig. 1 were found by tracing back from Case 1 and 2. Other probands were Case 4 and Case 6. Except in the last 3 generations no thorough efforts were made to trace the offspring of siblings of the ancestors to our probands in order to find further cases of GGM.

Qualitative estimation of urinary glucose was done with Clinistix® strips. The glucose tolerance of the parents of some patients was tested with oral doses of 50 g glucose. Blood glucose was measured by glucose oxidase method (10). The xcretion of amino acids in the urine was estimated quantitatively by the ninhydrin method. The pattern of amino acid excretion was studied by two-dimensional paper chromatography The necessary 24-hour pecimens of urine were obtained while the patients were under treatment and in a good nutritional state.

RESULTS

Genealogy

The pedigree of the patients with GGM (Fig. 1) has black symbols for known, diagnosed cases. Probable cases (hearsay evidence) have been represented by hatched symbols. The numerous intermarriages in the middle of the chart were brought about by the geographic isolation of the area in which these people were living. The patients, as well as the common ancestors to whom all the patients could be traced, belong to the white, European race;

charides is small and fructose is present in a higher concentration than glucose (14) In GGM the decreased absorption of glucose after sucrose hydrolysis (Table 7 Case 4) results in a higher intraluminal concentration of glucose than of fructose. The fact that in no experiment with a disaccharide does the absorption of glucose exceed $^1/_3$ of the amount released by hydrolysis (Table 7) contrasts also with the results obtained in perfusion studies on normal individuals. In the latter the main part of released glucose never appears in the lumen (15)

In a previous article (28) it was reported that patients with GGM are capable of splitting ingested disaccharides into monosaccharides. The findings in the stools of small amounts of disaccharide after lactose ingestion (Case 6) and after sucrose ingestion, as observed by Laplane *et al* (25) in one of their patients, indicate, however that disaccharide hydrolysis in patients with glucose-galactose malabsorption is not always complete. There is no deficient activity of disaccharidases in mucosal specimens from patients with GGM (1 3 37) Probably the most important factor allowing unsplit disaccharide to appear in the stools is the short intestinal passage time after administration of badly tolerated carbohydrates.

The intubation studies showed that glucose and galactose released from the disaccharides by the mucosal disaccharidases are given no opportunity to by-pass the defective transport mechanism Hence, if the metabolic block" is located at the entry step of the monosaccharides into epithelial cells, the most plausible location of the defect with regard to current concepts (37) the disaccharidases seem to exert their effect before complete penetration of the sugar through the cell membrane

SUMMARY

The histories of 6 cases 2 male and 4 female, with glucose galactose malabsorption (GGM) are presented. Of these, 4 have survived and are in good general health on a diet with a reduced carbohydrate content. One case died at 2 months of age with severe malnutrition due to intractible diarrhoea before a diagnosis was made. The other patient who died, was diagnosed and treated from the neonatal period, and he was progressing until infection occurred by a *Candida albicans* followed by death at 3 months of age in a picture of agammaglobulinaemia. One patient is now a woman of 41 The main symptoms are diarrhoea from birth, dehydration and malnutrition. Glucose is found in the watery stools and there is also a slight glucosuria. Hyperosmolar serum is often seen. Two patients, not those treated at an early stage, developed renal concrements probably owing to the long lasting water loss with the stools Treatment during the first months consisted of replacement of the ordinary dietary carbohydrates by fructose. Although the basic biochemical disorder lasts throughout life, limited amounts of starch and milk could be introduced later in infancy Some absorption of glucose could be demonstrated, tentatively due to a second pathway for intestinal glucose absorption which is apparently not shared by galactose. Hydrolysis of disaccharides occurred in the small intestine of GGM patients but the released glucose was absorbed no better than when administered as a monosaccharide. This implies that the site of disaccharidase activity is located more superficially at the luminal side of the epithelial cell membrane than the disturbed step of glucose and galactose transport.

ACKNOWLEDGEMENTS

From the cottage hospital of Stensele, Dr A. Frykholm referred Case 1 and Dr T Sawe referred Case 2. Case 4 was referred by Dr P G Bergfors, Skellefteå. The post mortem examination of Case 2 was performed by Dr B. Larsson and Professor C.-M Fajers, Umeå, and of Case 5 by Professor S. Falkmer and Dr L. Hassler Umeå. The histology of lymphoid tissues and the lungs of Case 5 were also examined by Dr G. Nathorst Windahl Uppsala. The authors are grateful to all these colleagues.

This work was supported by grants from the University of Umeå, the University of Lund, the Swedish Medical Research Council and the Swedish Nutrition Foundation.

Key words. Malabsorption, glucose, galactose, disaccharides, absorption tests, diet, hyperosmolar dehydration.

Acta Pædiat Scand Suppl 188 1969

GLUCOSE-GALACTOSE MALABSORPTION

A Genetic Study

K. MELIN and G. W MEEUWISSE

Department of Pediatrics, University of Umeå, Sweden, and Department of Pediatrics, University of Lund, Sweden

Glucose-galactose malabsorption (GGM) is, as described in the previous pages, a congenital disorder characterized by watery acid meliturhea from birth. Practically all the reported cases of GGM have a mild glucosuria, that of Dubois *et al.* (12) is an exception.

In a preliminary report we mentioned 3 related, female cases of GGM where the parents were all mutually related (31) GGM was concluded to be a recessively inherited disorder In a later communication a male case was reported (32) The present article contains a detailed pedigree. In order to find a method of detecting heterozygotes, biochemical investigations on carbohydrate metabolism were undertaken on parents of some of the patients with GGM. The pattern of amino acid excretion by the kidney was studied in five of the patients and their parents.

MATERIAL AND METHODS

The patients, coded 1–6 (Fig. 1), were presented with their case histories in the previous pages. Cases 2 and 5 died in the hospital at the age of 3 and 4 months, respectively Cases 1 4 and 6 are children, aged 10 7 and 6 years, respectively Case 3 is now woman of 42.

The pedigree has been made up from data gathered through numerous interview among relatives of the patients and from parish registers, of which photocopies are available at the city library of Umeå. The ancestors on the top of Fig. 1 were found by tracing back from Case 1 and 2. Other probands were Case 4 and Case 6. Except in the last 3 generations no thorough efforts were made to trace the offspring of siblings of the ancestors to our probands in order to find further cases of GGM

Qualitative estimation of urinary glucose was done with Clinistix® strips. The glucose tolerance of the parents of some patients was tested with oral doses of 50 g glucose. Blood glucose was measured by glucose xidase method (10). The xcretion of amino acids in the urine was estimated quantitatively by the ninhydrin method. The pattern of amino acid excretion was studied by two-dimensional paper chromatography The necessary 24-hour specimens of urine were obtained while the patients were under treatment and in good nutritional state.

RESULTS

Genealogy

The pedigree of the patients with GGM (Fig. 1) has black symbols for known, diagnosed cases. Probable cases (hearsay evidence) have been represented by hatched symbols. The numerous intermarriages in the middle of the chart were brought about by the geographic isolation of the area in which these people were living. The patients, as well as the common ancestors to whom all the patients could be traced, belong to the white, European race

---

Abbreviations: β-AIB, β-amino isobutyric acid, GGM, glucose-galactose malabsorption; GTT glucose tolerance test.

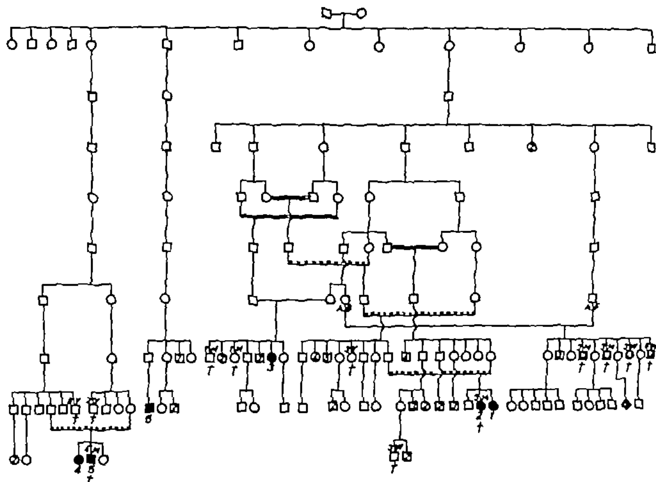


Fig 1 Pedigree of the six patients with glucose galactose malabsorption. All could be traced back to one sibship, born in the beginning of the 18th century *The numbers below the filled symbols* correspond with those of the case histories. Age at death of some individuals is indicated above their respective symbols. Numbers within symbols refer to the number of consecutive sibs of the same sex or unspecified sex (diamond). *Symbols*: ■, affected males ● affected females, □○ probable affected relatives with early death ═══ marriage between cousins, ═══ marriage between second cousins.

they are not Lapps.[1] The couple of common ancestors gave birth to 13 children in the beginning of the 18th century

Cases 1 and 2 are 3rd and 2nd children to parents who were second cousins in two ways. The father had a sister who was dwarfed and mentally retarded. She died at the age of 3 but there was no history of diarrhoea. The parents of Case 3 were third cousins In this family there were eight more children, two of whom died at about 1 month of age from pneumonia. They had no diarrhoea. The parents of Cases 4 and 5 are second cousins. A healthy 3rd child has recently been born to them. Both parents had a brother who died at a young age, without having suffered from diarrhoea. The father but not the mother of Case 6 could be proved to be a distant relative of the other patients with GGM. The mother's pedigree could no be completed beyond 5 generations.

In the last generation on the pedigree chart (Fig. 1) there is one boy who died at a cottage hospital from severe diarrhoea at 3 weeks of age. His maternal grandfather is a brother of the mother of Cases 1 and 2 The pedigree of the father of this infant has not been ascertained The boy was born at term in a breech

[1] In ancient times the north of Sweden was inhabited only by Lapps, a numerically small race with traits differing from the rest of the Swedish people. Swedes of other origin began to colonize the area in the 16th century

delivery At birth he was small for date and asphyctic, but for the first two weeks his condition was reasonably good, and breast-fed his weight increased from 1810 g to 2110 g. Vomiting and watery diarrhoea started when a cow's milk formula was introduced and this condition lasted one week until his sudden death. As the history during the first two weeks speaks against GGM, he is not regarded as a probable case of this disorder An aunt (A.G. in Fig. 1) of Case 3 married to a distant relative (A.F.), had 12 children 4 of them died between the age of 3 weeks and 3 months from intractable diarrhoea commencing in the new born period. They were all breast-fed. The mother of Case 3 had helped her sister to nurse these children, and she stated that the symptoms were identical to those of her own daughter Moreover the annotations in the parish registers were compatible with the diagnosis of GGM in 3 of these infants. In the 4th case there was no mention of the cause of death. According to information from relatives there were 2 more children in this family twins, who died in the same picture of watery diarrhoea at a few weeks of age. They however were not recorded in the parish registers.

Biochemical investigations

The parents of Cases 1 and 2, of Cases 4 and 5 and of Case 6, were repeatedly tested for glucosuria. Glucosuria after meals was found on two occasions only in the father of Cases 1 and 2. During an oral glucose tolerance test, when the blood glucose rose from 89 to 147 mg/100 ml in 30 minutes, no glucosuria occurred. The mother of these two girls and the parents of Case 4 had normal GTT's too. The other parents were not studied with a GTT

Examination of the urinary excretion of amino acids revealed that Cases 1 3 4 and 6 but not Case 5 excreted increased amounts of β-aminoisobutyric acid (β AIB) The total excretion of α-amino acids was normal. Amongst the parents, the father of Cases 4 and 5 and the mother of Case 6 excreted increased amounts of β AIB.The other parents excreted normal or undetectable amounts of this compound. β AIB excretion could not be investigated in the father of Case 3

DISCUSSION

Five of the cases of GGM, represented by a solid symbol in Fig. 1 belong to 3 sibships with a total of 15 children. In all these cases the parents were related to one another The sixth case of verified GGM is the only child of his parents. An ancestral relationship between these parents could not be proved. The father however is a descendent of the large family from which all other patients originate.

From the pedigree, containing both male and female cases, and from the fact that the parents are healthy with no history of chronic diarrhoea in childhood, it can be concluded that the disorder has an autosomal, recessive mode of inheritance. The literature is not at variance with this concept. The parents in the case presented by Nusslé and Gautier (40) are first cousins.

Laplane *et al.* (25) described two unrelated boys with GGM. A brother of one of them died from a disease with similar symptoms at 8 days of life, whilst a sister was healthy The other case had two healthy brothers. Anderson *et al.* (3) described a girl with GGM. Her brother died at 3 months of age in the same clinical picture. Single cases have been reported by several authors (1 12, 21 33–35 40 48) Some of these patients have healthy siblings.

Milk intolerance due to acquired lactase deficiency was found in the father of the case of Abraham *et al.* (1) It was considered incidental. The father of Nusslé's and Gautier's case had a history of chronic diarrhoea in childhood, but was found to be normal in adulthood. Symptoms suggestive of sugar malabsorption have not been present in the parents of other cases in the literature.

All published cases of the disorder have either been white ("Caucasian") or of unmentioned origin with one exception: the

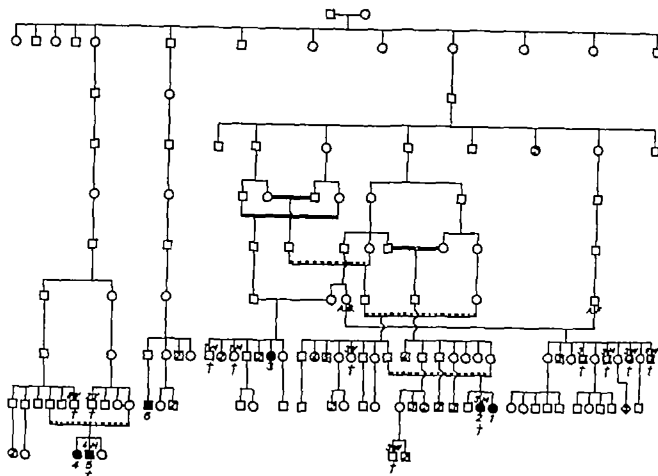


Fig 1 Pedigree of the six patients with glucose-galactose malabsorption. All could be traced back to one sibship, born in the beginning of the 18th century The numbers below the filled symbols correspond with those of the case histories. Age at death of some individuals is indicated above their respective symbols. Numbers within symbols refer to the number of consecutive sibs of the same sex or unspecified sex (diamond). *Symbols.* ■, affected males ● affected females, □● probable affected relatives with early death, ═══ marriage between cousins, ═══ marriage between second cousins.

they are not Lapps.[1] The couple of common ancestors gave birth to 13 children in the beginning of the 18th century

Cases 1 and 2 are 3rd and 2nd children to parents who were second cousins in two ways The father had a sister who was dwarfed and mentally retarded. She died at the age of 3 but there was no history of diarrhoea. The parents of Case 3 were third cousins. In this family there were eight more children, two of whom died at about 1 month of age from pneumonia. They had no diarrhoea. The parents of Cases 4 and 5 are second cousins. A healthy 3rd child has recently been born to them. Both parents had a brother who died at a young age, without having suffered from diarrhoea. The father but not the mother of Case 6 could be proved to be a distant relative of the other patients with GGM The mother's pedigree could no be completed beyond 5 generations.

In the last generation on the pedigree chart (Fig. 1) there is one boy who died at a cottage hospital from severe diarrhoea at 3 weeks of age His maternal grandfather is a brother of the mother of Cases 1 and 2. The pedigree of the father of this infant has not been ascertained. The boy was born at term in a breech

[1] In ancient times the north of Sweden was inhabited only by Lapps, a numerically small race with traits differing from the rest of the Swedish people. Swedes of other origin began to colonize the area in the 16th century

delivery At birth he was "small for date" and asphyctic, but for the first two weeks his condition was reasonably good, and breast-fed his weight increased from 1810 g to 2110 g. Vomiting and watery diarrhoea started when a cow's milk formula was introduced and this condition lasted one week until his sudden death. As the history during the first two weeks speaks against GGM, he is not regarded as a probable case of this disorder An aunt (A.G. in Fig. 1) of Case 3 married to a distant relative (A.F), had 12 children 4 of them died between the age of 3 weeks and 3 months from intractable diarrhoea commencing in the new born period. They were all breast-fed. The mother of Case 3 had helped her sister to nurse these children, and she stated that the symptoms were identical to those of her own daughter. Moreover, the annotations in the parish registers were compatible with the diagnosis of GGM in 3 of these infants. In the 4th case there was no mention of the cause of death. According to information from relatives there were 2 more children in this family twins, who died in the same picture of watery diarrhoea at a few weeks of age. They however were not recorded in the parish registers.

Biochemical investigations

The parents of Cases 1 and 2, of Cases 4 and 5, and of Case 6, were repeatedly tested for glucosuria. Glucosuria after meals was found on two occasions only in the father of Cases 1 and 2. During an oral glucose tolerance test, when the blood glucose rose from 89 to 147 mg/100 ml in 30 minutes, no glucosuria occurred. The mother of these two girls and the parents of Case 4 had normal GTT's too. The other parents were not studied with a GTT

Examination of the urinary excretion of amino acids revealed that Cases 1 3 4 and 6 but not Case 5 excreted increased amounts of β-aminoisobutyric acid (β AIB).The total excretion of α-amino acids was normal. Amongst the parents, the father of Cases 4 and 5 and the mother of Case 6 excreted increased amounts of β-AIB The other parents excreted normal or undetectable amounts of this compound. β AIB excretion could not be investigated in the father of Case 3

DISCUSSION

Five of the cases of GGM, represented by a solid symbol in Fig. 1 belong to 3 sibships with a total of 15 children. In all these cases the parents were related to one another The sixth case of verified GGM is the only child of his parents. An ancestral relationship between these parents could not be proved. The father however is a descendent of the large family from which all other patients originate.

From the pedigree, containing both male and female cases, and from the fact that the parents are healthy with no history of chronic diarrhoea in childhood, it can be concluded that the disorder has an autosomal, recessive mode of inheritance. The literature is not at variance with this concept. The parents in the case presented by Nusslé and Gautier (40) are first cousins.

Laplane *et al.* (25) described two unrelated boys with GGM. A brother of one of them died from a disease with similar symptoms at 8 days of life, whilst a sister was healthy The other case had two healthy brothers. Anderson *et al.* (3) described a girl with GGM. Her brother died at 3 months of age in the same clinical picture. Single cases have been reported by several authors (1 12, 21 33–35 40, 48). Some of these patients have healthy siblings.

Milk intolerance due to acquired lactase deficiency was found in the father of the case of Abraham *et al.* (1). It was considered incidental. The father of Nusslé's and Gautier's case had a history of chronic diarrhoea in childhood, but was found to be normal in adulthood. Symptoms suggestive of sugar malabsorption have not been present in the parents of other cases in the literature.

All published cases of the disorder have either been white ("Caucasian") or of unmentioned origin with one exception: the

father of the patient of Abraham *et al.* (1) was Chinese whilst the mother was Irish.

Including siblings who were at death not diagnosed as cases of GGM but who apparently suffered from this disease, the number of reported patients with GGM now amounts to 20 This relatively low figure, despite the fact that the disorder has been recognized for 6 years (25 28) indicates that the gene frequency is rather low The pedigree of our patients also speaks in favour of a low gene frequency: in only one case (Case 6) consanguinity could not be demonstrated, and this may be due to the fact that the pedigree of the mother became incomplete when traced back for more than a few generations. To our knowledge, only one more case of GGM has been diagnosed in Sweden in a different part of the country (21) A possible relationship with the patients of the family reported here has not yet been sufficiently investigated.

As mentioned in the beginning of this article, glucosuria seems to be a constant finding in the patients with GGM. As the glucosuria is slight, it has to be repeatedly looked for especially if only moderately sensitive methods like Clinistix® are used The parents who were examined disclosed no glucosuria except for one father where the occasional glucosuria seemed to have a pre-renal cause. GTT's performed on two couples of parents were normal. Hence, it was not possible to demonstrate carriers of the recessive gene by these methods. Incubation studies performed with biopsy specimens from the proximal jejunum of the parents of a child with GGM gave no evidence of reduced active transport of glucose into the mucosa of heterozygotes (37)

In order to investigate whether the patients with GGM have signs of tubular malfunction other than glucosuria, the urinary excretion of amino acids was studied. Although considerable confusion exists as to the causes of increased excretion of β AIB it can be said that it is probably not due to a decreased tubular reabsorption (5) Between 5 and 10 per cent of healthy adult Occidentals seem to have an increased excretion of β AIB as a recessively inherited trait (7 17) Among Orientals the percentage of "excretors" is about 25 per cent (5 7) The frequency of excretors in Occidentals has later been questioned (3) In children a large excretion of β AIB is fairly common. It has been found in connection with a variety of disorders, e.g. iron or iron-copper deficiency anaemia (7) Too little is known about the metabolic sources of this β amino acid for any conclusions to be drawn. Among other influences, nutritional factors are probably involved in nongenetic excretors (7) Mild liver disease has also been mentioned as a cause (5) Our patients showed no anaemia, no signs of malnutrition or liver malfunction when their excretion of amino acids was examined. An altered carbohydrate metabolism due to a subnormally low exogenous glucose supply and appreciable amounts of dietary fructose might have influenced this to some degree. With regard to the unspecificity of the increased β AIB excretion in children there is at present little reason to believe that four of our patients happened to belong to the group of genetical β AIB excretors. On the other hand no evidence can be put forward regarding any relation between the high excretion of β AIB and the disturbed transport of sugar in GGM.

SUMMARY

The pedigree of 6 cases (2 male and 4 female) of glucose-galactose malabsorption is presented. Besides the 6 cases seen by the authors, there occurred in the same pedigree at least 4 more instances of death in early infancy due to intractable diarrhoea. It is likely that these resulted from glucose-galactose malabsorption. The parents of the patients were healthy and had no history of chronic diarrhoea in infancy or thereafter As judged by oral GTT's on two pairs of parents they had normal glucose absorption. No renal glucosuria, present in all the patients, was found in the parents. It was concluded that glucose-galactose malabsorption

has an autosomal recessive mode of inheritance.

In 5 patients (from 4 different sibships) where the urinary excretion of amino acids was examined, 4 had increased excretion of β-aminoisobutyric acid although they were in a good nutritional state. Of 7 parents examined, 2 excreted increased amounts of the same compound. The finding of this selective aminoaciduria is probably incidental and, at least in the children, is not believed to be genetically determined.

ACKNOWLEDGEMENTS

The authors received the kind help of Dr R. Jagenburg (Dep. of Clinical Chemistry, Sahlgrenska Sjukhuset, Gothenburg) and had the advantage of his vast experience in evaluating the excretion of amino acids. Among the many helpful people giving valuable information on the pedigree, Mrs Jenny Arklind, Berg Umeå, has to be mentioned with gratitude. Part of the genealogic study of Case 6 was done by Mr K. Lundberg, Stockholm.

This investigation was supported by grants from the University of Umeå, the county authority (Västerbottens läns landsting) and the Swedish Nutrition Foundation.

Key words: Malabsorption, glucose, galactose, renal glucosuria, β-aminoisobutyric acid excretion, heredity

REFERENCES

1. Abraham, J. M., Levin, B., Oberholzer, V. G. & Russel, A.: Glucose-galactose malabsorption. *Arch Dis Childh, 42*: 592, 1967
2. Alnäs, A.: Alkalisk växtmaltosering såsom reagens på sockerhalt ... *Upsala Läkareför Förh, 2*: 472, 1866–67
3. Anderson, C. M., Kerry, K. R. & Townley, R. R. W.: An inborn defect of intestinal absorption of certain monosaccharides. *Arch Dis Childh, 40*: 1, 1965.
4. Anargos, J. H.: Intestinal absorption of hexoses in the dog. *Am J Physiol, 206*: 1095, 1964.
5. Armstrong, M. D., Yates, K. & Kakimoto, Y.: Excretion of β-aminoisobutyric acid by man. *J Biol Chem, 238*: 1447, 1963.
6. Bach, Ch., Thiriez, H., Schaefer, Ph. & Cayrocha, P.: Intolérance au saccharose chez un nourrisson. *Arch Franç Pédiat, 19*: 1138, 1962
7. Berry, H.: Symposium on hereditary metabolic diseases. Individual metabolic patterns: II. Excretion of beta-aminoisobutyric acid. *Metabolism Clin and Exptl, 9*: 373, 1960.
8. Burke, V. & Danks, D. M.: Monosaccharide malabsorption in young infants. *Lancet, 1*: 1177, 1966.
9. Csáky, T. Z. & Lassen, U. V.: Active intestinal transport of D-xylose. *Biochim Biophys Acta, 82*: 215, 1964.
10. Dahlqvist, A.: Determination of maltase and isomaltase activities with glucose-oxidase reagent. *Biochem J, 80*: 547, 1961.
11. Dahlqvist, A. & Borgström, B.: Digestion and absorption of disaccharides in man. *Biochem J, 81*: 411, 1961
12. Dubois, R., Loeb, H., Eggermont, E. & Mainguet, P.: Étude clinique et biochimique d'un cas de malabsorption congénitale du glucose et du galactose. *Helv Paediat Acta, 21*: 577, 1966.
13. Gomori, G.: Preparation of buffers for use in enzyme studies. *In:* Colowick, S. P. and Kaplan, N. O., *Methods in enzymology, Vol. I.* Academic Press, New York 1955.
14. Gray, G. M. & Ingelfinger, F. J.: Intestinal absorption of sucrose in man: Interrelation of hydrolysis and monosaccharide product absorption. *J Clin Invest, 45*: 388, 1966.
15. Gray, G. M. & Santiago, N. A.: Disaccharide absorption in normal and diseased human intestine. *Gastroenterology, 51*: 489, 1966.
16. Hagedorn, H. C., Halström, P. & Jensen, N.: Hurtige metoder till bestemmelse af blodsukker ved kaliumferricyanid. *Hospitalstidende, 206*: 1095, 1935
17. Harris, H.: Family studies on the urinary excretion of β-amino-isobutyric acid. *Ann Eugenics, 18*: 43, 1953
18. Heyrovsky, A.: A new method for the determination of inulin in plasma and urine. *Clin Chim Acta, 1*: 470, 1956.
19. Holdsworth, C. D. & Dawson, A. M.: The absorption of monosaccharides in man. *Clin Sci, 27*: 371, 1964.
20. Hydén, S.: A turbidometric method for the determination of higher polyethylene glycols in biological materials. *Ann Agr Coll* (Sweden) *22*: 139, 1955.
21. Kuijper, K. & Ockerman, P. A. (to be published).
22. van de Kamer, J. H., ten Bokkel Huinink, H. & Weyers, H. A.: Rapid method for the determination of fat in feces. *J Biol Chem, 177*: 347, 1949
23. Kern, F. & Struthers, J. E.: Intestinal lactase deficiency and lactose intolerance in adults. *JAMA, 195*: 927, 1966.
24. Kern, F., Struthers, J. E., Atwood, W. L. & Shapiro, L. J.: Lactose intolerance as a cause of steatorrhea in an adult. *Gastroenterology, 44*: 836, 1963.
25. Laplane, R., Polonovski, C., Etienne, M., Debray, P., Lods, J.-C. & Pissarro, B.: L'intolérance aux sucres à transfert intestinal actif. Ses rapports avec l'intolérance au lactose et le syndrome coeliaque. *Arch Franç Pédiat, 19*: 895, 1962.

26. Launiala, K. The mechanism of diarrhoea in congenital disaccharide malabsorption. *Acta Paediat Scand 57* 425 1968
27 Laws, J W & Neale, G Radiological diagnosis of disaccharidase deficiency *Lancet* 139 1966.
28. Lindquist, B & Meeuwisse, G W. Chronic diarrhoea caused by monosaccharide malabsorption. *Acta Paediat Scand 51* 674 1962.
29 — Intestinal transport of monosaccharides in generalized and selective malabsorption. *Acta Paediat Scand Suppl 146* 110 1963
30. — Diets in disaccharidase deficiency and defective monosaccharide absorption. *J Am Diet Ass 48* 307 1966
31 Lindquist, B., Meeuwisse, G W & Melin, K. Glucose-galactose malabsorption. *Lancet 2* 666, 1962.
32. — Osmotic diarrhoea in genetically transmitted glucose-galactose malabsorption. *Acta Paediat Scand 52 217 1963*
33 Linneweh, F., Schaumlöffel, E. & Barthelmai, W. Angeborene Glucose und Galaktose Malabsorption. *Klin Wschr 43* 405 1965
34 Liu, H Y Tsao, M U Moore, B F Giday Z. & Anderson, G Intestinal and renal malabsorption of monosaccharides. *Abstracts Amer Pediat Soc* p. 42, 75th Annual Meeting, Philadelphia 1965
35 Marks, J F., Norton, J B & Fordtran, J S. Glucose-galactose malabsorption, *J Pediat 69* 225 1966.
36. Meeuwisse, G W (Unpublished results).
37 Meeuwisse, G W & Dahlqvist, A. Glucose-galactose malabsorption. A study with biopsy of the small intestinal mucosa. *Acta Paediat Scand 57* 273 1968
38. Meeuwisse, G W & Lindquist, B. Glucose-galactose malabsorption. The intermediate metabolism of carbohydrates. (In preparation).
39 Newey H. Absorption of carbohydrates. *Brit Med Bull 23* 236, 1967
40. Nussle, D & Gautier E. Malabsorption congénitale du glucose et du galactose. *Assemblée ann Soc Suisse Pédiat* Lugano, juin 1966.
41 Nylander E. Über alkalische Wismutlösung als Reagens auf Traubenzucker im Harne. *Ztschr Physiol Chem 8* 175 1883–84.
42. O'Brien, D & Ibbott, F A. *Laboratory Manual of Pediatric Micro- and Ultramicro Biochemical Techniques*, 3rd ed., p. 240. Harper and Row New York 1962.
43 Polonovski, C. & Gombault, P Valeur du test au D-xylose en pédiatrie. *Sem Hôpit, 38* 419 1962.
44 Prader A., Auricchio, S. & Mürset, G. Durchfall infolge hereditären Mangels an intestinaler Saccharaseaktivität (Saccharoseintoleranz). *Schweiz Med Wschr 91* 465 1961
45 Robinson, H. M. C. & Rathbun, J C. Electrophoresis of free sugars in blood. *Science 127* 1501 1958
46. Roe, J H The determination of sugar in blood and spinal fluid with anthrone reagent. *J Biol Chem 212* 335 1955
47 Salomon, L. L., Allums, J A. & Smith, D E. Possible carrier mechanism for the intestinal transport of D-xylose. *Biochem Biophys Res Comm, 4* 123 1961
48. Schneider A. J Kinter W B & Stirling, C. E. Glucose galactose malabsorption. Report of a case with autoradiographic studies of a mucosal biopsy *New Engl J Med 274* 305 1966.
49 Smith, H. W. *The Kidney Structure and function in health and disease* Oxford Univ Press, New York 1951
50 Somogyi, M. Determination of blood sugar *J Biol Chem 160* 69 1945
51 — Notes on sugar determination. *J Biol Chem, 195* 19 1952.
52. Stiller D Histochemical demonstration of the resorption of xylose from small intestine. *Nature 209* 924 1966.
53 Winberg, J Renal function studies in infants and children with acute, nonobstructive urinary tract infections. *Acta Paediat Scand 48* 577 1959

(G W.M.)
Barnkliniken
Lasarettet
Lund
Sweden